Adaptive Sensorimotor control for navigation

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Adaptive Sensorimotor control for navigation

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To Saba,
for all the joy you bring me.

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The rodent whisker system as a model to study sensorimotor integration

The sense of touch is one of the prominent sensory modalities that help form the neural representations of our worlds. Mice and rats, due to their nocturnal habits and living environment, commonly utilize touch to navigate, locate and/or discriminate objects (*1*). Among the touch receptors in the body, those embedded in the whisker follicles are particularly of interest to whisking rodents, as they sweep their whiskers in the air to examine their surroundings. The perceived sensory signals by the whiskers are transmitted through brainstem and thalamus into the barrel cortex: a highly developed part of the sensory cortex in rodents devoted to the spatiotemporal representation of whisker touch (*2*). The barrel cortex of rodents has emerged as an excellent model system to study active sensory processes and sensorimotor integration. Because rodents start whisking at the end of the second postnatal week, the barrel cortex of neonatal rodent is also an attractive system to investigate the effect of early cortical activity during the developmental period and maturation of sensorimotor integration.

The somatosensory cortex of rodents is extensively used to study sensory information processing due to its unique relationship between the vibrissae and the barrel columns: each whisker on the snout transmits tactile information to one particular barrel in layer 4 of the primary somatosensory cortex (*1*). This one-to-one relationship provides the opportunity to correlate the physical information obtained at the vibrissae, with its corresponding neural representations in the cortex (*3–5*). Whisker deflection upon contact with a tactile surface (touch) is detected by the mechanoreceptors within the whisker follicles and transmitted through the infraorbital nerve into the brainstem. This sensory signal travels further into the thalamus and finally reaches the whisker-related somatosensory cortex (*1*, *4*, *6*). The layer 4 (L4) of the cortex receives the main input from the thalamus among this six-layered structure. Woolsey and Van der Loos (*7*) in 1970 characterized the so-called barrel cortex in L4 of somatosensory cortex in mice, which takes its name from the barrel-shaped structures that are recognisable when taking a tangential section through layer 4 upon staining with cytochrome oxidase, a mitochondrial enzyme enriched in the thalamocortical projections originating from the thalamus (*7*). The barrels and their associated cortical columns are somatotopically organized as such neighboring columns in the periphery are represented by the neighboring cortical columns in the primary somatosensory cortex.

The rodent barrel cortex provides a useful model to investigate the neural network mechanisms underlying the sensory processes, structure, organization, plasticity and development of the neocortical column. This is due to the combination of practical experimental advantages and its similarity to other cortical columnar structures: the barrel cortex is located superficially and its cortical column can be identified easily

in vivo and in vitro (*8–10*), the sensory periphery (whiskers) can be manipulated (trimmed, passively deflected, etc) and the resulting mechanical forces at the follicle can be estimated using mathematical analysis of the whisker shape and deformation (*11–13*), single neurons in a specific barrel column can be monitored and manipulated in vivo using e.g. electrophysiology and optogenetic (*4*, *14*) specific neuronal cell types located in a selected cortical layer can be targeted by genetic manipulations (*15*).

In this chapter I review the whisker sensorimotor system, starting with feedforward and feedback pathways and nuclei involved in the sensory processing. Then, I look at the whisker control motor-related pathways, specifically focusing on the anatomical connections between the sensory and motor nuclei and their cellular organization. In the last part, I review the postnatal development of the barrel system and the role of serotonin in its development and function. A part of this content has been submitted for publication (*2*) .

THE WHISKER-BARREL SYSTEM STRUCTURE

Tactile sensory information perceived by the mechanoreceptors, located in the follicle, passes through several centers in the nervous system including the dorsal root ganglion, the brainstem, the thalamus, and ultimately projects to the cortex (Figure 1). This sensory processing system consists of parallel pathways that transfer the information from snout to cortex, each with distinct input-output organization. Data suggests that these pathways serve different roles in processing and relaying the signal (*6*, *16*, *17*). While the information ascends towards higher processing areas in the cortex in a bottom-up fashion, it passes through multiple interconnected structures which suggests processing loops connecting the sensory and motor circuits (*2*, *18*). Processing of complex information in the primary somatosensory whisker-related cortex is performed by laminar and columnar interactions across the six layered neocortical columns. These columns are defined morphologically as an extension of the ‘barrel’ structure within L4 across the supragranular layers above L4 (i.e. L1-3) and the infragranular layers (i.e. L5-6) below. A great number of studies have revealed many aspect of this complicated processing system, however, yet an overall understanding remains elusive.

Vibrissal Follicle Innervation

Vibrissal follicles are innervated by two distinct neuronal pathways in animals that whisk: superficial pathway (SVN) and a deep pathway (DVN) (*19*). These pathways have

distinct projections to the trigeminal complex. Superficial Vibrissal nerves (SVN) terminate in the upper regions of the inner-conical body and form neural rings. Deep vibrissal nerve terminates in the mid-lower region of the inner-conical body (*20*). The absence of SVN is observed in animals that do not whisk, which argues that SVN might be specialized in transmitting proprioceptive signals related to vibrissa motion (*21*).

Superficial and deep vibrissal nerves target distinct areas within the brainstem trigeminal complex of rodents. The trigeminal complex has four main nuclei: Principalis, Oralis, Interpolaris, and Caudalis. Principalis and Interpolaris constitute two major sensory pathways designated as lemniscal and paralemniscal respectively. Both lemniscal and paralemniscal pathways receive somatotopically organized input from the DVN (*22*). Most SVN axons terminate in Caudalis, but a few also innervate Principalis but these projections are not somatotopically organized (*22*, *23*).

Lemniscal pathway

The lemniscal system is the primary whisker-to-barrel sensory pathway. Through this pathway, the information from whisker follicle transmits via the infraorbital nerve by primary afferent neurons to the trigeminal ganglion (see Figure 1). The trigeminal ganglion projects to the principal nucleus of the trigeminal nuclei (PrV) in the brainstem, and thereafter, the information flows to the ventral posterior medial (VPM) thalamic nucleus, where VPM neurons project to the cortex (S1). In the lemniscal pathway, the topographic representation of the whisker pad can be distinct in each stage, from whisker pad to barrelets in brainstem, to barreloids in the thalamus and finally to barrels in the primary somatosensory cortex (S1) (*2*).

The receptive field organization and the topographical representations are preserved throughout the lemniscal pathway, from brainstem to cortex. The trigeminal ganglion neurons respond to the whisker deflection with a short latency and encode whisker deflection direction, amplitude and velocity (*24*, *25*). Neurons in brainstem (Prv) and thalamus (VPM) mimic the response of their prior afferent nuclei, although they have larger receptive fields and lower response magnitude (*26*, *27*). The L4 of barrel cortex fires action potentials by a delay of 2-4 ms after thalamus, however, have smaller receptive fields, and respond sparsely to whisker deflection. This transformation might be a key to determine the computational principles that lead to sense of touch (*28–30*). All in all, the mechanical information in a whisker follicle is relayed in a spatially and temporally precise manner in the lemniscal pathway, and response transformations occur at each level.

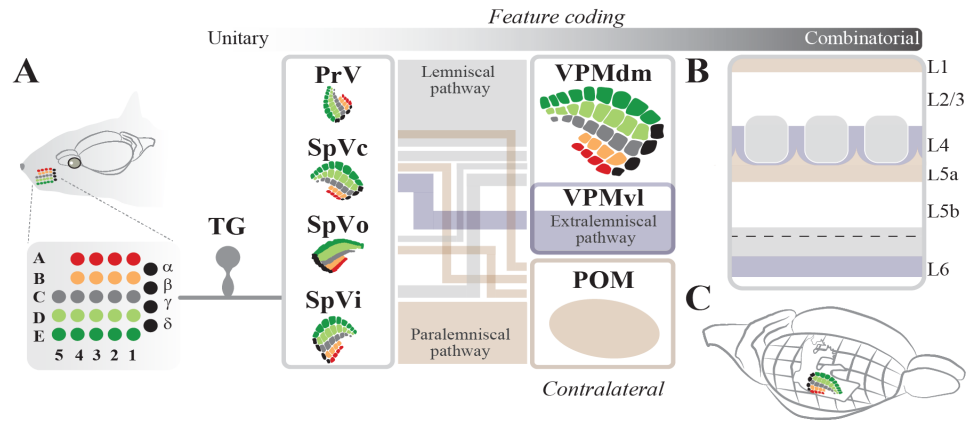

FIGURE 1. A simplified representation of the whisker-to-barrel cortex pathway which encodes, transforms and transfers the sensory information from the periphery to the cortex. This somatosensory axis creates the neural representations of the tactile world. Adapted from (2). See the main text for details. Note that the color code for circuit connectivity specifies the approximate terminal locations for each pathway.

The feed-forward projections in the lemniscal pathway mostly innervate L4 as they reach the barrel cortex (*31–33*). L4 neurons project to the superficial layers, layers 2 and 3 (L2/3). L2/3 neurons primarily project to superficial layers of neighboring barrel columns, other cortical areas, and/or descend into L5 within the same barrel-related column (*10*). L5 neurons heavily project to numerous areas mostly out of cortex such as striatum, thalamus, and/or brainstem. Secondary somatosensory cortex and primary motor cortex send strong projections to L5 and L6 in S1. L6 excitatory afferents come from L4 and L5 within the same column, and other L6 neurons. L6 projects to VPM, posteromedial thalamic (PoM) and other cortical areas, such as the primary motor cortex (M1) and S2 (*1*, *34*).

Paralemniscal pathway

The second ascending pathway involved in whisker sensorimotor processes is the paralemniscal pathway that involves brainstem, thalamus and cortex. Besides PrV, trigeminal ganglion projects to the subnucleus interpolaris division of the trigeminal nucleus (SpVi) in brainstem (see figure 1). The posteromedial (PoM) thalamic nucleus receives afferent from SpVi and projects to S1 and to the primary motor cortex (M1). Unlike the lemniscal pathway that enables rapid (short latency) bottom-up propagation of sensory information, majority of sensory projections to PoM comes from S1 and with a large latency (*35–37*). Receiving projection from S1 cortex and projecting to M1 suggests a sensorimotor integration role for PoM (*38*).

Projections originating from PoM and targeting the barrel cortex, like other non-VPM projections, largely avoid barrels and innervates either superficial and/or deep layers in S1 or the inter-barrel septa in L4: thalamocortical axons from PoM neurons heavily target L5A and L1 (*34*, *39*).

Besides lemniscal and paralemniscal pathways, subnucleus caudalis (SpVc) n trigeminal nucleus project to VPM and form extralemniscal pathway (see figure 1) which carries information about whisker contacts (*6*, *40*).

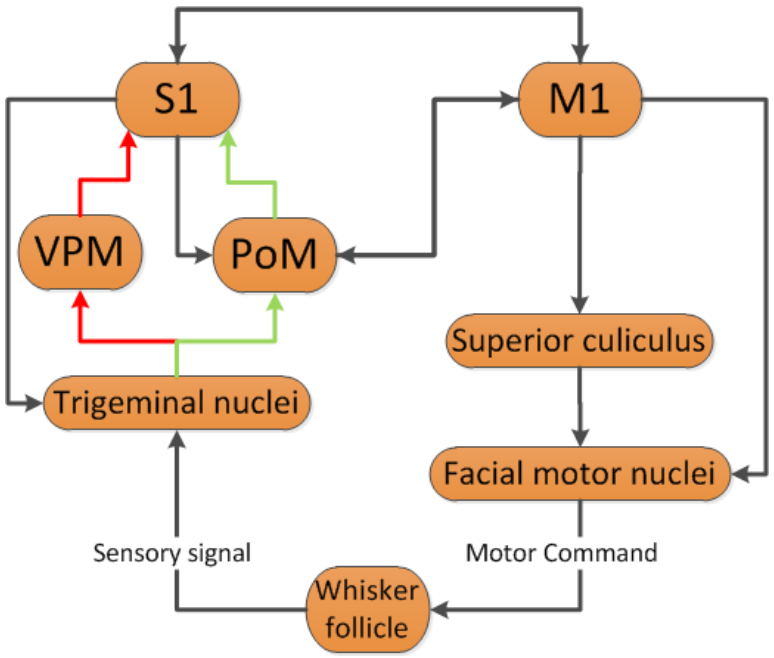

FIGURE 2. Simplified diagram of the sensorimotor loop. Only the Lemniscal (red) and Paralemniscal (green) pathways are shown. See (*6*, *41*, *42*) for detailed reviews on sensorimotor circuits in the rodent brain.

Feedback projections

Besides feedforward projections discussed above, whisker related sensory system involves series of feedback afferents to lower nuclei in the hierarchy (see figure 2). S1 sends cortical feedback to PrV and SpVi in brainstem and to VPM and PoM in thalamus. Moreover, S1 projects to other midbrain and brainstem structures including the superior colliculus, pons, and the spinal cord (*1*). These feedback control systems, next to the feedforward information flow construct a complicated interconnected control system that governs the whisker sensory computation.

Main corticothalamic feedback projections originate from L5 and L6 in S1. L5 efferents reach PoM, while L6 efferents target VPM and/or PoM. Studies suggest two different roles for these pathways. L5 excitatory projections rapidly adapt to repetitive whisker deflections, while L6 projections tend to facilitate upon repetitive activation (*1*). L6 mediated facilitation, however, might be topographically constrained as local pharmacological activation of L6 in a single column enhances sensory responses in aligned barreloids while causing suppression of activity in non-aligned barreloids (*43*). It may propose a 'driver' role for L5 and a 'modulator' role for L6 (*44*). L5 can be considered as a part of the feedforward system, acts as a gate to pass the information, and L6 as a part of the feedback loop. However, yet the contribution of these corticothalamic pathway in sensory processing is unclear (*34*). Both SpVi and PrV in the brainstem receive projections from S1 (*34*), but only projections onto SpVi are topographical (*45*, *46*).

Secondary somatosensory cortex (S2)

Whisker-related secondary somatosensory cortex (S2) is located in the parietal cortex posterolateral to the barrel cortex in S1. Vibrissal S2 is also somatotopically organized and occupies 14% of the total area of the S2 (*23*, *47–50*). In relation to barrel cortex, receptive fields of S2 neurons are larger, whisker evoked responses are relatively weaker; onset latencies of S2 neurons are comparable to S1 neurons but the former show stronger direction selectivity (*51*). VPM, PoM, barrel and septa columns project to S2 (*52–56*). There are reciprocal connections between barrel cortex and vS2 like M1 and S2 reciprocal projections (*54*, *57*). S2 projects to the striatum, the pontine nuclei, VPM and PoM (*23*, *58*).

Motor system and control of whisker

Active touch requires the integration of motor and sensory systems. Efferent signals (the motor commands) give rise to rhythmic motor activity that creates stereotypical whisking behavior (*59*). Whisker movement generates robust reafference (sensory) signals that track vibrissa motion and touch (*60–62*). One of the cardinal questions in systems neuroscience is to determine the role(s) of internally generated motor commands to perception.

A large area of motor cortex in rodent represents the facial motor muscles, including those connected to whisker follicles. Anatomical studies have shown monosynaptic connections between vibrissal M1 and several subcortical nuclei (*58*, *63*, *64*). It has been suggested that higher-order areas initiate and/modulate active whisking mo-

vement, however the rhythmicity of the whiskers is caused by a brainstem central pattern generator (*6*). Physiological evidence argues that activity in vibrissal M1 is correlated with whisker movement and it increases prior to whisking onset (*65*); indicating a role of M1 in initiating and modulating whisking (*6*, *66*, *67*). On the other hand, rhythmic whisking persists after inactivation of vibrissal M1, although whisking kinetics is changed (*68*). The signal generated in M1 ultimately passes through lower nuclei to reach facial motor nucleus which process and relay the information coming from M1 to the whiskers. There is also a sparse, but direct M1 projections, to motor neurons in the facial nucleus (*69*), but most M1 corticofugal axons innervate other brainstem nuclei, such as the reticular nucleus and superior colliculus, that in turn innervate the facial motor nucleus (*58*, *63*, *64*).

Most of the vibrissal cortical areas are reciprocally connected. Vibrissal M1 is connected to the barrel cortex, S2 and M1 in the contralateral hemisphere (*70*). Barrel cortex-M1 reciprocal projections are the main sensorimotor cortical connections, originating mainly from L2/3 and L5a and targeting mostly the deeper layers but also L1 and the septal regions in L4 of S1 (*71–73*). S1 projections are most probably the main source of sensory information for M1, next to the strong afferents from S2 (*57*, *74*, *75*). The M1 efferent reach S1, S2 and collateral M1 (*58*, *76*).

Multiple ipsilateral thalamic nuclei project reciprocally to M1: the mediodorsal group of nuclei (MD), the centrolateral group (CL) and the PoM (*58*, *77–79*). Besides, M1 projects to other thalamic regions ipsi- and contralaterally including to the inner anteromedial (IAM), the anteromedial (AM) and VPM (*58*, *77–79*) thalamic nuclei. As mentioned in the previous section, it has been proposed that M1 projections to PoM may play a role in gating of ascending sensory information.

Besides thalamus, M1 projects to other subcortical regions such as the pontocerebellum (*80*), dorsolateral neostriatum (*81*), intermediate and deep layers of the superior colliculus (*58*) and the claustrum (*82*). Many of these postsynaptic targets of M1 projections also receive sensory projections originating from the barrel cortex, thus sensorimotor information converge multiple times along cortical and subcortical pathways.

CELLULAR ORGANIZATION OF THE BARREL CORTEX

Barrel cortex is complex circuit that consists of variety of cell types whose integrative properties, including input-output relationship with the rest of the brain, plausibly

govern the sense of touch. Approximately 80-85% of the barrel cortical neurons are excitatory and remaining are inhibitory (*34*). Excitatory neurons' projection target both distant nuclei, e.g. barrel cortex to vM1 projections, as well as the other neurons in their vicinity, let it be a cortical column or layers. Majority of inhibitory neurons project locally within or across layers in vS1. The role of each cell type in the network dynamic is unknown. However studying their behavior is of great importance to understand the system.

Main excitatory neurotransmitter in the central nervous system is the glutamate. The main glutamatergic neurons in S1 are spiny stellate, star-pyramidal, and pyramidal neurons, which their morphologies and connectivities in the barrel system are well studied (*3*, *83–87*). VPM and other L4 neurons project to spiny stellate neurons in L4 (*88*) and the spiny stellate cells project to superficial layers within the same barrel column (*85*). Star-pyramidal neurons in L4 have similar morphology to spiny stellate cells, while their projections are mainly vertical across the barrel layer (*84*). Most of the cells in cortical Layer 2/3, 5, and 6 are pyramidal neurons. These neurons mostly project to other layers within the ipsilateral barrel cortex or cortico-cortically to contralateral S1, M1, or S2 (*86*).

The inhibitory neurotransmitter Gamma-aminobutyric acid (GABA) is released from interneurons which is comprised of a diverse population of neurons (*87*). GABAergic neurons can be subclassified based on active and passive membrane properties, axonal and dendritic projection patterns, and the molecular markers (mostly calcium binding proteins) they express interneurons can be classified based on the cluster analysis (*89*). Besides, interneurons in L2/3 can be grouped into seven groups based on their dendritic excitability, including basket cells, chandelier cells, double bouquet, bitufted, Martinotti cells, Cajal-Retzius cells and neurogliaform cells (*1, 90*).

Given the diversity of the cell types, subclasses, their columnar distribution and pattern of projections (both afferents and efferents) one goal in systems neuroscience is to describe the sensorimotor integration for each cell-type in a cortical column and layer resolution. Although advancements in targeting single cell populations for optogenetic neural control is now broadly utilized, understanding the principles of sensorimotor control at the neuronal level will necessarily requires targeted modulation of the top-down neuromodulatory neurotransmitters (e.g. serotonin, dopamine, norepinephrine (noradrenaline)) which control the neuronal processing in a context specific manner.

POSTNATAL DEVELOPMENT OF THE BARREL CORTEX

Normal development of brain is associated with a time span termed “critical periods” in which nature and nurture jointly ensure orderly development of neural organization and function. Animal behavior is determined through animals’ interaction with the environment and the developmental regulation of the genetic code. Maturation of cortical area in charge of a certain behavior depends on the experience-dependent neuronal processes together with experience-independent molecular mechanisms. Altered circuit development results in irreversible alterations in the organism, impairing function also in adulthood. The concept of critical period was first studied in the ocular dominance plasticity studies in cats, where depriving afferent input to one eye immediately after birth causes irreversible loss of visual acuity and shift in the organisation of V1 cortical columns (*91–95*).

Maturation of cortical areas arises due to the combination of molecular cues within the cortex and neuronal activity-dependent cues provided by sensory projections from the thalamus (*93*). Molecular mechanisms predominate at early stages of network formation, while activity-dependent processes modulate it at later stages of development (*91*). Network development in the barrel system in rodents and its topographic representation has been extensively studied. The barrel formation starts at E9 (prenatal) and its maturation continues to (p21) postnatal; the initial formation of the network relies on molecular cues, however the refinement of its topography depends on neuronal activity (*93*).

The critical periods for the somatosensory system is firmly related to the developmental phases for corticogenesis and cortical innervations. The intrinsic genetic programs determine cortical arealization (*96*). Thereafter, thalamocortical axonal (TCA) innervation to the cortical plate is governed by molecular cues, intrinsic activity (*93*), and neuromodulatory systems including the serotonergic system (*97*). TCA projections govern the functional characteristic of the primary sensory areas. Activation of thalamic efferent to S1 during development shapes the barrel patterns and network during postnatal development (*93*). Whisker manipulation (e.g. plucking, trimming, sparing or exposure to enriched environment to increase utilization of whiskers) during the critical period, induces plastic changes in the size of the barrel cortical area and its network architecture (*39*). It has been suggested that subplate (SP) neurons participate in sensory map formation through TCA targeting and patterning. They innervate subcortically to the primitive striatum where they reach TCA project and superficially to transiently target layer IV (*98*, *99*). Once TCA projections reach the assigned cortical territories, neural activity therein is vital for the anatomical and functional development of the sensory areas (*93*).

TCAs communicate with their postsynaptic neurons through glutamatergic neurotransmission which is regulated by monoamines (such as serotonin) while GABAergic projections shape overall excitation to inhibition ratio in the network(*100*). Genetically modified animal models targeting serotonin showed that changes in serotonin homeostasis results in permanent changes in adult behavior and alters the brain neural network. Different serotonin receptors at different developmental stages affect various developmental processes such as neurogenesis, apoptosis, axon branching and dendritogenesis (*97*). These modulations causes irreversible changes in the network.

Barrels appear after TCA projections and cortical sensory areas form. The clustering of L4 neurons around TCAs is seen as early as P3 and matures by P7 (*39*, *101*). From P10-14, TCA projections fine tune their structures and their innervation of the layer IV barrel neurons (*102*). With the initiation of active whisking around P14 central pattern generators located in the brainstem start controlling the whisker motor fibers on the snout (*103*). The pattern of GABA immunoreactivity reaches maturity in the third week (P16– P21) as the receptive field of excitatory neurons and their axodendritic projections reach “maturity” by P21 (*102*, *104*). Therefore P21 onwards the barrel cortical neurons are considered to be mature (*105*).

These developmental processes in the critical period are crucial for normal neural structure/function. However, this period is not a closure to plasticity and changes in the neural structure and network. An essential property of sensory maps is to adapt to changes and optimize the processes which continues after P21.

THE SEROTONERGIC SYSTEM: A KEY REGULATOR OF SENSORIMOTOR CIRCUIT DEVELOPMENT

Whisker sensorimotor system is shaped during early postnatal brain development by neuromodulatory neurotransmitters and in particular by the three principal monoaminergic neuromodulators: serotonin (5-HT), dopamine and norepinephrine (noradrenaline). Among them the contribution of serotonin (5-HT) to the development of sensorimotor circuits are best studied.

The first indirect evidence of serotonin playing a role in the development of the somatosensory cortex was the observation of transient serotonergic innervations, overlapping the layer IV barrel pattern during the first postnatal weeks (*106*, *107*). Further studies suggested that altered development of monoaminergic systems leads to malfunction in sensorimotor function and sensory perception (*108*), in particular during the first 3 weeks of the postnatal development, during which sensorimotor circuits mature (*109*, *110*).

Serotonin (5-HT) that is released in the barrel cortex is synthesized in the raphe nuclei of the brainstem (see Figure 3). Dorsal and median part of the raphe nuclei project to multiple targets making the serotonin an important player in many central processes such as regulation of emotion (amygdala), cognitive functions (prefrontal cortex), sleep, sexual and eating behavior (hypothalamus), learning and memory (hippocampus), as well as sensorimotor perception/action (the brainstem, thalamus, spinal cord, sensory and motor cortices) (*108*). The availability of the serotonin is regulated by the serotonergic release as well as the rate of clearing from the synaptic cleft by the presynaptic 5-HT transporter (SERT). The SERT protein terminates serotonin signaling and recycles it in a sodium-dependent manner while monoamine oxidase A (MAOA) mediated the degradation of 5-HT in the presynaptic neurons (*111*).

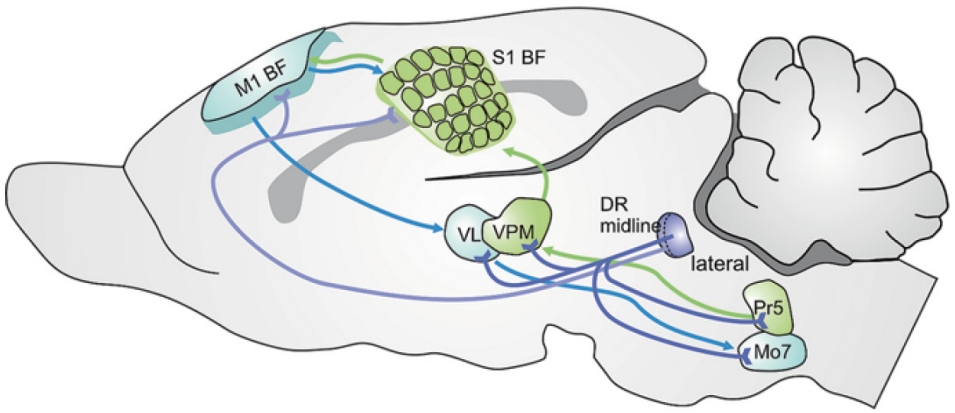

FIGURE 3. Simplified overview of the serotonergic innervation along the rodent whisker sensorimotor axis. Dark blue and purple shows the main origins and projections of the serotonergic system targeting the sensorimotor system. Dorsal Raphe (DR) nucleus projects to S1 and M1 in cortex, to ventrolateral (VL) and ventral posterior medial (VPM) in thalamus, principal trigeminal nucleus (Pr5) and facial motor nuclei (Mo7) in brainstem. Green shows the the lemniscal pathway and main processing structures of this somatosensory system and light blue shows the motor processing units and their related projections to thalamus (VL) and brainstem (Mo7) (adapted from (*108*)).

Serotonergic modulation of sensorimotor function might be mediated by various subcortical and cortical networks (see Figure 3). Dorsal raphe (DR) projects to both ipsilateral S1 and M1, the principal trigeminal nucleus (Pr5) in the brainstem and the ventral posterior medial (VPM) as well as ventrolateral nucleus (VL) in the thalamus (*112*, *113*). Because DR nucleus neurons also innervate collateral facial motor nuclei (Mo7) in the brainstem (*114*) serotonergic release by DR could potently alter sensorimotor processes throughout the sensorimotor axis. These wide range of axonal projection also suggests multiple modulatory roles for DR including synaptic integration and regulation (brainstem and thalamus) together with signal processing and signal propagation (cortical sensorimotor networks). Beside the proposed modulatory role of serotonin in the mature brain, the change in innervation pattern and number of collaterals during brain development also suggest that serotonergic system might be involved in the development of the sensorimotor circuits (*115*).

Serotonergic neurons in the raphe nuclei project to brain regions starting already from E11-15 (*109*, *110*, *115*). During the first three weeks after birth, the density of serotonergic axon arborisation in the cortex and number of their synapse into cortical areas increase. During the first two postnatal weeks, serotonergic axons form dense clusters in S1 L4 (barrel structures) reaching their peak at P7, as thalamocortical projections mature. By the end of the second postnatal week, the density of the serotonergic projections gradually reduce. The hyperinnervation by DR serotonergic neurons coincides with the critical period of cortical network formation in the barrel cortex. Because activation of HT1B receptors, which are located on the thalamic axonal projections targeting cortical L4, impairs the probability of glutamate release (*116*, *117*), serotonergic neurotransmission can shape propagation of information originating from the sensory periphery. Blockage of the serotonin uptake by the serotonin transporter during this period results in impaired thalamocortical innervation and the organization of the barrels in the L4 (*97*, *118*), as well as reduction of GABAergic signalling molecules critical for inhibitory synapse formation (*119*). These results argue that serotonergic neuromodulation during the first weeks of postnatal development controls the propagation of the sensory input along the thalamocortical network by both modulating the excitatory feed-forward drive along the thalamocortical projections and the cortical inhibitory drive. Considering this period of postnatal development also coincide with onset of whisking (around P12-P14) serotonin might powerfully shape the functional maturation of the active whisking and adaptive motor control in the whisker system.

THE OUTLOOK

Understanding the fundamental principles of sensorimotor computation is one of the cardinal questions in systems neuroscience. The present work takes advantage of the well studied rodent whisker system to address the behavioral and computational principles of adaptive whisking, a popular model of sensorimotor computation. Here, I investigate the object localization as a sensorimotor process and specifically address:

In **Chapter 2,** I deploy a custom robotic apparatus to train animals on an object localization task. This robot enables us to train animals and later perform experiments in environments where the sensory environment is dynamically modified while animals performing the object localization task. To comprehend the mechanisms of sensorimotor computations an essential step is to quantify the sensory input and motor output behaviorally. In our whisker system model this could be achieved by quantifying whisking characteristics (such as whisker position, frequency, amplitude, velocity) and capture the touch statistics (e.g. touch position, contact induced displacement of whiskers, touch duration). This robotic platform is equipped with high-speed imaging and motion sensing that enables precise quantification of sensorimotor behavior. Using the robot to train rats and mice across various experimental conditions, here I present a big dataset that is made publically available. The data presented herein could be used in describing the principles of sensorimotor computation during navigation as exemplified in chapters 3-4.

In **Chapter 3**, I address the development of the sensorimotor computation in tactile object localization task. Nature and nurture together architect organization of cortical neural networks throughout life. In particular the first three postnatal weeks are critical for the anatomical, functional and behavioral maturation cortical circuits. In this chapter I study the development of sensorimotor computation in juvenile rats (~P21) and after they reach adulthood (~P65) while they performed a tactile object localization task. Here, I first show how various parameters of whisking and body locomotion as building blocks of sensorimotor computation matures through time. Then, I introduce a holistic model which simulates object localization computation by whiskers. Using this mode, I demonstrate that object localization is an adaptive motor control problem, in which brain uses learned transfer functions to translate sensory information into motor action to generate adaptive sensing during goal-directed action.

In **Chapter 4**, I look into serotonin as one of the cardinal influencers on network formation, during and after developmental period. Based on the results in the previous

chapter adaptive motor control of whisker position for goal-directed action develops postnatally after the maturation of intracortical circuits. During and after developmental period, changing serotonin level could potentially alter the maturation of sensorimotor computation. Altering sensorimotor network connectivity in turn changes signaling in the network, and could potentially alter the maturation of sensorimotor computation. In this chapter, I investigate this hypothesis in serotonin transporter knock-out animals and after transient intervention with serotonin signaling during postnatal development. Using a heuristic graph-based computational model of whisking system, I attempt to explain the minimum circuit requirements for adaptive control of whisker position and predict how changes in this network affects sensory experience.

Finally, **Chapter 5** summarises all the observations and proposes a novel view of the adaptive whisker positional control. Here, I suggest that the brain utilizes sensorimotor computation as a filtering process. It implements the *filter* iteratively by dynamically updating its internal model of the body, world as well as the body in respect to world. This computation ultimately enables two way communication between the body and the world.

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2

An open-source high-speed infrared videography database to study the principles of active sensing in freely navigating rodents

Active sensing is crucial for navigation. It is characterized by self-generated motor action controlling the accessibility and processing of sensory information. In rodents, active sensing is commonly studied in the whisker system. As rats and mice modulate their whisking contextually, they employ frequency and amplitude modulation. Understanding the development, mechanisms and plasticity of adaptive motor control will require precise behavioral measurements of whisker position. Thanks to the advances in high-speed videography and analytical methods, it is now possible to address these questions from a big-data perspective, by collecting and analysing large datasets for high-dimensional quantification of behavior. Here we provide a dataset of 6642 videos as hundreds of freely moving juvenile (3rd-4th postnatal week) and adult (P65+) rodents explored their environment in darkness to locate a stationary tactile object while being constrained on an elevated platform. The dataset includes sensory exploration with single- or multi-whiskers in wild-type animals (rat and mice), serotonin transporter knock-out rats, rats that received pharmacological intervention targeting serotonergic signaling. The dataset includes varying background illumination conditions and signal-to-noise ratios (SNRs), ranging from homogenous/high contrast to non-homogenous/low-contrast. A subset of videos has been whisker and nose tracked, and are provided as reference for image processing algorithms. The behavioral data can be directly used to study (1) development of sensorimotor computation, (2) top-down mechanisms that control sensory navigation and whisker position, (3) cross-species comparison of active sensing. It could also help to address contextual modulation of active sensing during touch induced whisking in head-fixed versus freely behaving animals. And finally, it provides the necessary data for machine learning approaches for automated analysis of sensory and motion parameters across a wide variety of SNRs with accompanying human observer determined ground-truth.

DATA DESCRIPTION

Context

Whiskers, or mystacial vibrissae, are sensory hairs that are densely organized as a grid on the snout. Rats and mice actively move their whiskers in an oscillatory motion to explore their environment as they integrate sensory information spatiotemporally across whiskers and whisk cycles (*1–5*). The motor control of whisker position is a result of sensorimotor computation where sensory information collected during the last ~3 whisk cycles is used to plan the whisker motion for the subsequent whisk cycle (*6*). Although animals can perceive passive touch before the onset of whisking (*7*), it is not known when and where in the brain the sensorimotor computation for adaptive motor

control for whisker position emerge. Moreover, the mechanisms responsible for the development and plasticity of sensorimotor computation are largely unknown. Because sensorimotor integration is contextually regulated (*8–12*), altered by the change in neuronal excitability along the sensorimotor circuits (*13*) and based on experience and the current state of the sensory organs (*1*), identification of the principles of sensorimotor computation will require large scale behavioral experiments where sensory input on whiskers and motor control of whisker position are studied at high spatiotemporal resolution. Here we introduce the first iteration of such a dataset as freely moving rodents locate a tactile target under infrared light. The dataset includes independent variables of species (rat vs mouse), developmental age (juvenile vs adult, i.e. 3-5 postnatal weeks and >6 weeks, respectively), sensory deprivation (single vs multi whisker) and genetic background (i.e. SERT knock-down vs control, see below). The database might serve researchers across a broad range of disciplines, including cellular, behavioral, systems, cognitive neuroscience, and ethology, biomimetics, robotics, artificial intelligence, computer vision and active sensing communities, to study and model the principles of active sensing.

Animals

All experiments have been performed according to the Dutch law concerning animal welfare and the guidelines for the care and use of laboratory animals upon institutional ethical committee approval. All efforts have been made to minimize animal suffering and discomfort, and all precautions were taken to reduce the number of animals used.

The experiments were performed on 38 male rats and 10 male mice. Rats were either genetically engineered or pharmacologically treated to alter serotonergic neurotransmission, a neuromodulatory neurotransmitter that contributes to motor control (*14*), stimulus encoding in the barrel cortex (*15*), and is believed to modulate development and maturation of sensorimotor circuits (*16*). Experiments in rats also included corresponding wild type and vehicle injection controls. Mice were on the C57Bl6 background (B6;129P2-Pvalbtm1(cre)Arbr/J, The Jackson Laboratory, RRID:MGI:5315557). Parvalbumin neurons in this line express Cre-recombinase but the mice were otherwise not genetically or pharmacologically altered. The founder line was outcrossed to C57Bl6 for 20+ generations before the start of experiments. All mice were studied between 2-4 months of age.

Serotonin transporter knockout rats (Slc6a41Hubr) were generated on a Wistar background by N-ethyl-N-nitrosurea (ENU)-induced mutagenesis as described before (*17*).

Experimental animals were derived from heterozygous 5-HT transporter knockout (5HTT$^{-/-}$) rats that were outcrossed for 12+ generations with wild-type Wistar rats obtained from Harlan Laboratories (Horst, The Netherlands). Ear punches were taken at the age of 21 days after weaning for genotyping and 5HTT$^{-/-}$ and 5HTT$^{+/+}$ rats were randomly assigned to SERT KO (N=14 rats) and WT groups (N=14 rats), respectively.

5-HT transporter deletion alters neural function starting from embryonic brain development (*17*). Thus, in a second group of rats, we interfered with the serotonergic system after birth, and only transiently when serotonergic innervations appear in the barrel cortex [9]. Fluoxetine hydrochloride (10 mg/kg/day, Sigma Aldrich), a selective serotonin reuptake inhibitor, was dissolved in water and administered orally. Age matched dams in a separate cage received tap water and were considered as Vehicle controls. The fluoxetine administration started after birth (P1) and continued for 7 days, corresponding to the period of postnatal development critical for the maturation of thalamocortical projections (*18*). The pups of all groups (Fluoxetine, N=5; Vehicle, N=5) were kept together with their mothers until weaning.

Animal handling and behavioral observations

Animal behavior was studied as they located (or attempted to locate) a tactile target under infrared light between postnatal days (P) 21-P30, i.e. as juveniles, and/or after they reached sexual maturity (Figure 1). Animal handling protocols were similar to those employed previously (*1*, *6*, *8*, *13*). Experiments started with a familiarization session (20 min/animal) where P18 pup (in rats) or adult mouse subjects were introduced to the experimenter and the experimental room the first time. Habituation to the set-up consisted of two 20 minute sessions under no visible light but with white noise. The training sessions (N=10/rat; N=30/mouse) lasted 30 minutes (or 30 successful trials) in which the gap distance (see below) was randomly drawn from a Gaussian distribution. With increasing number of sessions, the mean of the distribution was increased and variance reduced, adapting each animal's individual learning curve, to ensure animals preferentially use their whiskers for target localization in majority of the trials. The set-up was cleaned with ethanol between sessions.

One day before the sessions that required animals to perform the task with a restricted set of whiskers, animals were anesthetized using isoflurane. Half of the animals received whisker plucking sparing a single (C2) whisker or single (C) row bilaterally; the other half received "sham plucking" during which they were handled similarly to the whisker deprived animals, however their whiskers were left unplucked. Whisker regrowth was assessed every day, and if needed whisker plucking was repeated.

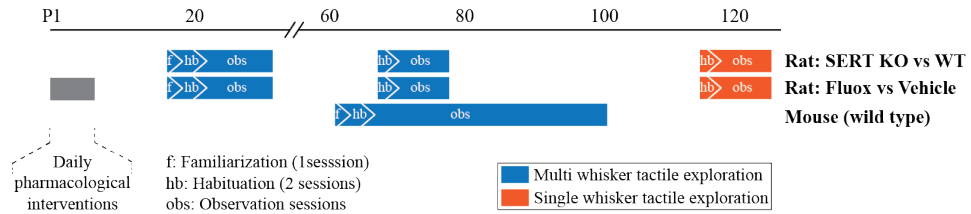


FIGURE 1. The timeline of experiments and handling. See main text for details.

The behavioral paradigm: Tactile object localization

We observed animals, under infrared light, as they shuttled between two elevated platforms with a variable gap-distance in between them. The animals were not food deprived; neither did they receive any reward for successful task execution. In this, so called spontaneous gap-crossing task (*1*, *6*, *8*, *13*), the distance between the platforms is varied to enable observation of whisker dependent tactile object localization. In our training protocols, the gap-distance was randomly selected from a normal distribution whose mean increases and variance reduces with repeated training (i.e. increased number of training sessions) as described before (*15*). Catch trials, where the target platform is positioned just outside of the animal's reach, were randomly introduced (~15% of successful trials) to ensure that the task execution required tactile exploration and was not a result of expectation and sensorimotor habit formation.

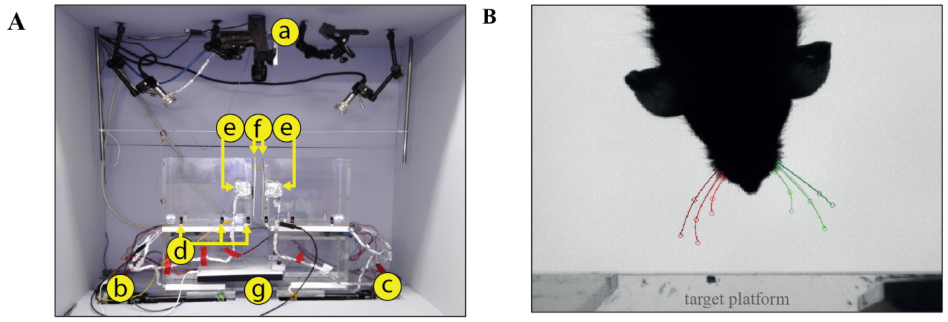
The experimental set-up and data acquisition

The experimental set-up consists of two elevated platforms and a high-speed camera that are mobilized by linear actuators (Figure 2A). The animal position on the platforms are tracked using motion sensors. Motion sensors also provide real-time feedback for robotic actions including closure of doors, limiting the animal's access to the gap, gating the sequence that control the position of tactile targets, triggering the streaming of high-speed videography data to disk, repositioning the camera to ensure optimal field-of-view independent from the target location, and, if required, delivery of the reward.

Each session starts with the experimenter positioning the animal on one of the two platforms. The task of the animal in any given trial is to locate the other platform, if it is within tactile reach. The success on the task is defined as the animal traveling between the two far ends of the platforms, as assessed by motion sensors in real-time. If an animal starts and returns to the same starting position without interrupting the middle motion sensor on the other platform, the trial is classified as a failure. Animals are allowed to visit the gap as many time as they require before making a decision

on whether or not to gap-cross. Upon decision, the door attached to the only access point of the platform that the animal is located upon is closed and the target platform is positioned in its new position as described above.

Animals' sensorimotor behavior as they attempt to locate the target is recorded using a high-speed camera. The camera is mobilized using a linear actuator to ensure comparable field of view across trials. An infrared backlight is positioned below the gap to provide the necessary contrast for imaging (Figure 2B).



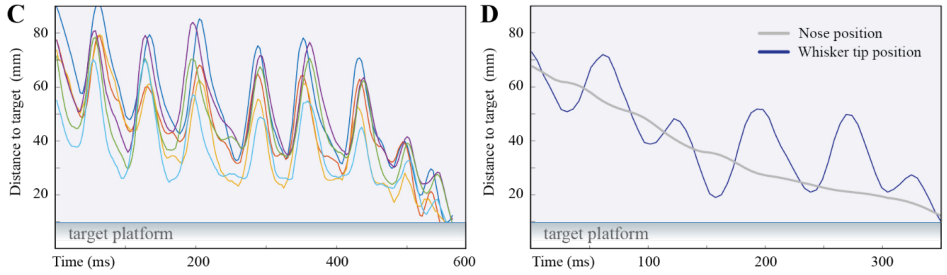


FIGURE 2. Experimental set-up and sample behavioral data. (A) The experimental set-up is installed in a sound attenuated chamber. Three linear actuators (a-c) mobilize a high-speed camera and tactile targets. Infrared motion sensors (d; 3x/platform) provide positional information about the animal and gate all actuators. Servo motors (e) installed at the ends of the platforms by the gap mobilize PVC panels (f) that act as gates. Gates are closed between trials and during tactile target motion. A custom made infrared (890 nm) panel provide background illumination for the video recordings. **(B)** A sample still image with human observers' ground truth data about whisker positions are overlaid. Images were acquired at either 480fps with a resolution of 512x640 (110 microm/pixel) using a PointGrey Flea3 (FLIR, Germany) camera (in mice) or at 220fps (240x320 pixels; 625 microm/pixel) using an AVT Pike (Allied Vision, Germany) camera (in rats). **(C)** Whisker tip position for 6 whiskers as a rat located the target. Each color corresponds to one whisker. **(D)** Similar to C but for single whisker along with the corresponding trace of nose position.

The videography data can be used to track body and whisker position in high spatiotemporal resolution. To provide the ground-truth data for future machine learning approaches for whisker tracking, three human observers tracked whisker and nose position in a non-overlapping subset of videos (>150 tracked frames/video). Corresponding raw data are provided in .mat (MATLAB) format, see Figure 2C and 2D for sample traces, see Supplemental Table 1 for list of files that include ground-truth tracking data. If animals made multiple attempts to locate the target, which is common especially during the early phases of object localization training (*1*), the human observers were instructed to focus on the last epoch of exploration.

Data format and online database organization

All video files are stored as 4D matrices in .mat files as well as .mp4 files for streamlined navigation in standard browsers. The .mat formatted data can be visualized using "implay" function in the Image Processing Toolbox or using the standard "movie" function in MATLAB. Movies can be converted to other formats using built in functions "movie2avi" or "videowriter". The videos can be manually or automatically segmented using open source software[1]. The dataset is available online at https://goo.gl/rooNk9 and distributed under Creative Commons BY (attribution alone) license. This is an open access license without any restriction on the copy, distribution or data display. Users can freely derive from the dataset but are kindly requres to cite the data source, i.e. the publication that announced the dataset (Azarfar et al, Gigascience, revised). The database is mirrored on Gigascience servers (DOI to appear upon publication).

The hierarchy in the data organization is shown in Figure 3 and include, in a descending order, species (rat vs mouse), age (juvenile vs adult), sensory exploration with single or multiple whiskers (e.g. single row or all whiskers intact) and transgenic, methods of intervention with serotonergic signaling along with corresponding controls. A tabulated excel document (available for download at https://goo.gl/rooNk9 and as Supplemental Table 1 in the published version of this article) provides the metadata about the experimental details including date of experiment, session and trial numbers, gap-distance, trial outcome (success vs failure), and whether the ground truth data is provided.

Application scenarios

This database will help to address numerous fundamental questions in systems neuroscience, including but not limited to (1) development of sensorimotor computation,

1 Matlab Whisker Tracker (github.com/DepartmentofNeurophysiology/Matlab-Whisker-Tracker) VideoViewer (bitbucket.org/benglitz/controller-dnp/downloads/)
DeepLabCut (github.com/AlexEMG/DeepLabCut)

(2) top-down mechanisms that control sensory navigation and whisker position, (3) cross-species comparison of active sensing. By comparing the sensorimotor exploration across wild-type juvenile and adult animals one could address how adaptive control of body and whisker position develop. Because adaptive motor control of whiskers is likely to be an outcome of a vector computation that ensures spatial constancy despite the coupled changes in the body [2], developmental changes in body positional control in respect to whisking might unravel the sequential development of motor control. Repeating the same analysis across SERT KO, Fluoxetine and the corresponding control animals would help to address the role of serotonin in shaping motor development and consequences of altered serotonergic signaling in sensorimotor control in adulthood. Finally, by comparing the sensorimotor exploration between the multi-whiskered rats and mice one could address cross-species differences in adaptive motor control during object localization.

The data provided could serve the on-going machine learning efforts that will ultimately allow automated segmentation of whiskers in near real-time, i.e in temporal resolution shorter than the duration of a whisk cycle. To ensure the usability of the database as a training set, we have included ground-truth data from a subset of video recordings. Understanding the principles of active sensing in biological systems might help to instruct adaptive solutions for artificial systems to adapt sensory navigation to the ever-changing motor demands of the navigating agent.

Limitations

Freely behaving animal experiments are often burdened by high-dimensionality and the associated sampling limitations. Even if animals execute behavior in a constrained environment, e.g. exploring a stationary target while standing on an elevated platform, as in the behavioral experiments described herein, animals could change their approach angle, kinematics of whisking, duration of exploration, number of whisker used to sample the target, head angle and head elevation among other variables across different trials. Previous studies quantifying the sensory, motor and perceptual behavior during whisker based object localization showed that both rats and mice perform spontaneous gap-crossing in a stereotypical manner and that ~100 trials (10 trials/animal) is sufficient to gather reproducible statistics of sensory and motor behaviors (*1*, *6*, *8*, *13*, *15*, *19*). Thus the current dataset with 6642 independent observations across 11 independent conditions (including species, age, genetic, pharmacological and sensory deprivation interventions) should provide sufficient sampling to address fundamental questions outlined in the previous section. However, we would like to attract the attention of the reader that the dataset does not include data from female animals.

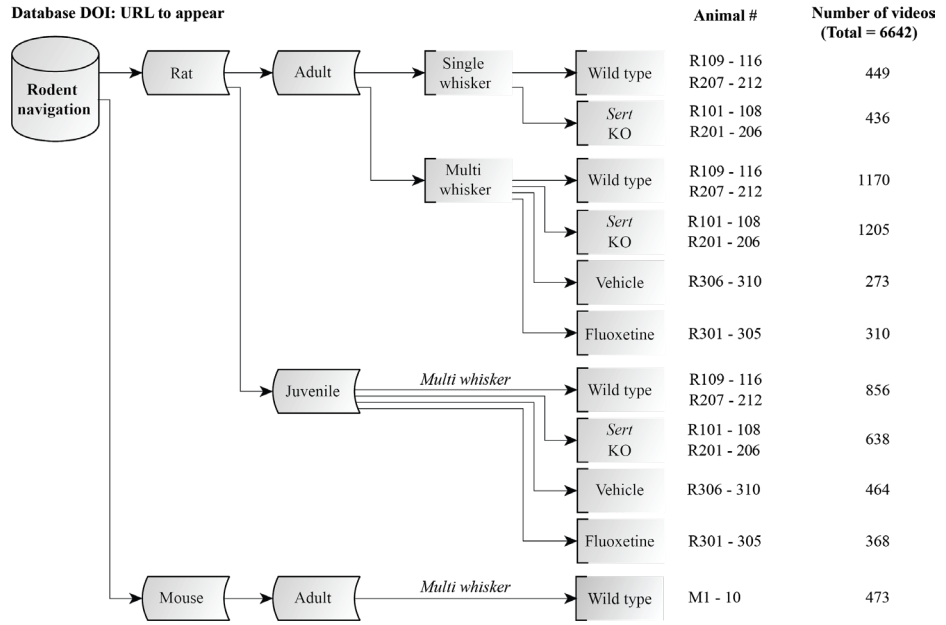


Figure 3. Organization of the dataset. See main text for details.

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3

Development of adaptive sensorimotor control for active sensing

Navigation is a complex sensorimotor computation which requires integration of allocentric and egocentric information. In darkness, rodents commonly rely on their tactile senses, in particular to their whiskers, to gather sensory information and instruct navigation. In this active sensing process, motor commands are adaptively regulated based on prior sensory information. This sensorimotor adaptation is implemented by independently controlling body and whisker position. The development of cortical neural networks during the first three weeks after birth is critical for the maturation of sensorimotor computation as animals gain their mobility and actively start collecting sensory information. However, whether sensorimotor computations for adaptive motor control develop during this period is unknown. Here, I addressed this question in rats longitudinally, during the last week of postnatal development and in adulthood, as freely behaving animals searched for a stationary target in darkness. The results showed that juvenile rats are capable of successful object localization but the adaptive sensorimotor strategies mature later in life. Adult rats adaptively control the mid-point and amplitude of whisking, and employ mature goal-directed locomotion strategies to perform sensorimotor computation, whereas, juvenile rats lack adaptive motor control of whisker position based on the recent sensory information. Computational modelling of the adaptive whisking argues that emergence of reactive retraction, i.e. whisker retraction that depends on sensory feedback and ensures constancy of duration of tactile sampling, participates in the development of adaptive sensorimotor control for active whisking.

INTRODUCTION

Rodents predominantly rely on sense of touch to navigate in darkness. Actively whisking rodents, e.g. rats and mice, highly depend on their whiskers (vibrissae) due to their nocturnal habits and sub-terrenial habitat in the wild. The sensory information collected by whiskers are transmitted through brainstem and thalamus into the barrel cortex, a sub region of the primary sensory cortex in rodents (*1*, *2*). During active whisking, motor commands are iteratively updated based on the prior sensory information, propagating through the sensory axis (*2–4*). The motor controls are adaptively regulated to enhance sensory acquisition, and thus reinforce sensorimotor computation and perception.

In the whisker system, the adaptive sensorimotor control is gated by whisker touch and regulates the spatiotemporal pattern of whisking (*3*). In rodents this process takes about 90 ms and requires integration of the sensory information acquired over the last three contacts with the target (*4*). The end result of this computation is the protraction of whiskers to the position where the animal thinks the target object is located (*4*).

Motor dynamics of whisker positional control is not the only parameter that governs sensorimotor computation during navigation. Body position and head angle are iteratively controlled to optimize tactile navigation. Locomotion and postural aspects of navigational sensorimotor computation (how the animal supports, moves, and controls particular body parts) develop alongside the maturation of relevant neural circuitry (*5–7*), similar to whisking behavior (*8–13*).

Coincidental to the development of cortical neural networks (*14*), most behavioral aspects of sensorimotor computation matures by the third postnatal week. Rat pups exhibit a flutter response to passive whisker contacts starting from P3 (*15*). They can retract their whiskers starting from P4 and protract them P7 onwards (*13*). Active whisking emerges around the second postnatal week (*12*). Thereafter, whisking gradually increases in frequency and amplitude, and reaches the adult form by the end of the third week (*12*, *13*, *16*) as animals start whisking in a stimulus dependent manner (*17*). Complimentary changes in the body positional control also appear during this period. Prior to P11, whisker movements are largely limited to unilateral retractions followed by head turns (*12*). Between P11 and P13 bilateral whisking develops along with enhanced forward locomotion and improved control of the head (*12*). Contact-induced modulations of whisking symmetry, synchrony, and whisking amplitude modulation emerge shortly thereafter and continue to develop at least until ~P18 when adult-like

locomotion patterns, such as rearing, develops.

Considering that both body and whisker positional control mature in parallel, it's tempting to speculate that sensorimotor computations in the whisker system emerge by the end of third week. Here, I experimentally addressed this question using publicly available high-speed videography recordings of rats performing a tactile object localization task (*3*, *4*, *18–21*). Rats performed object localization first as a juvenile (P21) and later as adults (~P65). Quantitative analysis of whisking, body position and tactile exploration showed that juvenile animals fail to utilize sensory information to drive adaptive motor control of whisker position. They continue whisking without altering the whisk amplitude and set-points in the whisk cycle. Adult rats, however, perform motor computation based on recent sensory information to adaptively control the mid-point and amplitude of whisking. Computational simulations of the active and adaptive motor control of whisker position argue that the brain must utilize a neural code that allows reactive retraction of whiskers that keep the duration of contact roughly constant across touch events. I propose that emergence of the reactive retraction and the modulation of the whisker protraction are essential for maturation of adaptive motor control.

MATERIALS AND METHODS

The experiments in this chapter were performed using 11 male wistar rats. To ensure the data is not confounded by repetitive sensorimotor training at large gap-distances (see below) and that it comes from a single day, we constrained the data to <3 trials/animal (N=30 per age condition). Animal handling, behavioral observations and behavioral experiment paradigm were as described in Chapter 2. In short, on the spontaneous gap-crossing task (*3*, *4*, *18*), animals shuttled between two elevated platforms with a variable gap-distance in between in darkness (Fig.1A). A mobilized high-speed camera recorded animals behavior during tactile object localization. Gap-distance was randomly selected from a normal distribution.

Automated analysis of tactile exploration statistics

All images were analyzed in MATLAB. A background image was selected before the animal entered the field of view and was subtracted from all subsequent frames. Platform edges were detected in the background picture as the transition points on a back-lit background. To determine the head angle, a triangle was created between the two ears and nose. Deviation of the nose from head center (between the ears) was

used to calculate the head angle. Whiskers were tracked manually (N=6 whiskers/animal; N=3 whiskers/snout) (Fig.1B,C). Whisker tracking was performed in animals which had all of their whiskers intact. Angular disposition of the base of the whisker was analyzed temporally and spatially (in respect to body-to-target position, i.e. nose to edge of the target platform (Fig.1A)). The speed with which animals approached the platform was quantified using the time derivative of the distance between the animal's nose and edge of the target platform. Frequency of whisking was calculated using FFT (Fig.2A) and cycle duration (i.e. the time it takes for the whisker to travel between two protraction set-point; Fig.2B). Gap-crossing was defined as the moment the animal's nose has passed the platform edge by more than 6 mm. Videos were then grouped by age and gap distances. The minimum gap distances of the analyzed movies were 14.5 cm for adult and 9 cm for juvenile, i.e. whisker distances. These distances were selected to ensure that only tactile exploration of whisker touch was quantified, as animals also use the touch receptors around their nose in shorter gap-distances (*3*, *4*, *18–21*). Whisker protraction was quantified in respect to the mid-point of the whisk space which was defined by the most protracted and retracted positions within the field (Fig.1D)

RESULTS

Quantitative analysis of the interplay between motor controls and sensory acquisition strategies will help to unravel the principles of sensorimotor computation. Here, using localization of stationary targets by freely behaving animals as a model system, I describe the development of adaptive motor control in the whisker system.

Motor strategies for tactile navigation across development

On the gap-crossing task, animals navigate between two elevated platforms with a variable distance between them in darkness (*3*, *4*, *18–21*). They extend their body over the gap to reach the tactile target using their whiskers (Fig. 1A). To analyze animals' locomotive strategies, I studied the speed at which they approach the target in the rostrocaudal orientation. This maneuver towards the target is a goal directed behaviour that minimizes the relative distance to the target, maximizing the likelihood of first contact with the target. The data shows that locomotion aspect of object localization develops in later ages in rats.

Spatially resolved speed of approach to the target shows that juvenile animals do not vary the speed of approach (Fig.1E, top) although adult animals approximately double

their speed every 100 ms prior to ~400 ms to gap-cross (Fig.1E, bottom). Although this approach profile could be interpreted as juvenile rats navigate towards the target without adapting their search strategy, increased mobility could be also be a by-product of non-motor variables (e.g. change in exploration vs exploitation strategies during development).

In both groups of animals whisker tip position correlates with the relative distance to target. Whisker tip position in relation to target (d_w) is determined by body position to target and whisker positional control. Analysis of whisker tip position in respect to target (d_n) revealed that whisker tip position converges to the tactile target in both juvenile and adult animals as the animal approaches to the target (Fig.1F). To decode the contribution of whisking motor pattern modulations on the sensorimotor computation, angular disposition at the base of the whisker during the task was studied.

Adaptive whisking sensorimotor control develops postnatally and matures after P21. Angular disposition at the whisker base is a principal component of the egocentric motor control strategies. Rats actively control their whiskers to augment the collected information by adaptively setting their whiskers protraction and retraction angle. Here, I studied the whisker protraction angle to evaluate these strategies. The whisking patterns were screened throughout each trial to determine the maximally protracted and retracted positions, middle of this range was set as zero degree set-point (also called mid-point, or whisker position at rest (*3*, *4*, *18–21*)). The protraction angle (**α**) in each trial was calculated in respect to the zero degree set-point. The results (Fig.1G) showed that adult mice position their whiskers more rostrally (bring them forward) as they approach the target. Juvenile animals, on the other hand, do not regulate their whisker protraction based on their relative distance to the target.

Frequency and amplitude modulation across development

In active sensing, sensory exploration is contextually modified in a task and goal specific manner. Adjusting whisking frequency is one of the factors that regulates adaptive control of sensory acquisition and integration in the whisker system (*22–25*). Berg and Kleinfeld (*26*) reported an increase in the whisking frequency range when animals change their whisking mode from ‘exploratory’ (range 5–15 Hz) to ‘foveal’ whisking (15–25 Hz) in search for reward. However, it is not yet known whether tactile sampling strategies adapt after the first contact with the target. Considering that the higher the whisking frequency, the shorter the duration of tactile exploration at a given whisk cycle, reduction in whisk frequency during tactile exploration will maximize the contact duration.

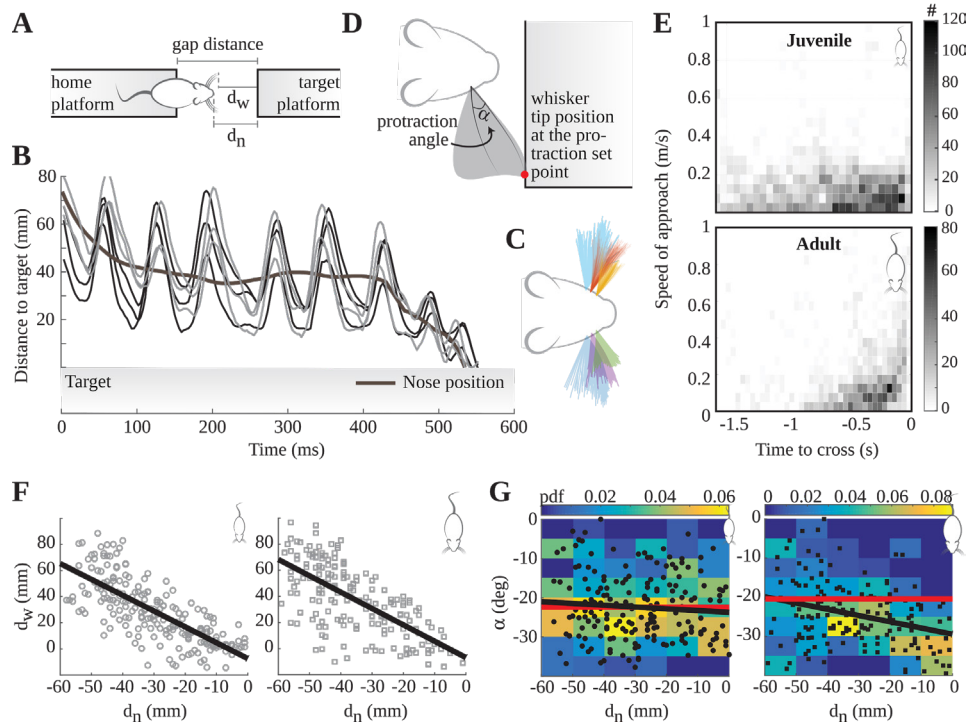

FIGURE 1. Motor strategies for tactile navigation across development. (A) The Gap-crossing paradigm (d_n : nose distance to target, d_w whisker’s tip distance to target). **(B)** An example representative dataset of target position, animal position, approach curve and whisker tracking results. **(C)** Overlay of the tracked whiskers. Data from a single trial is shown. **(D)** Graphical representation of the protraction angle (**α**). Grey shaded area represents the most protracted and most retracted whisker positions during a trial, normalized to the change in the body and head position. **(E)** Speed of locomotion during the last 1.5 seconds prior to gap-crossing. The upper figure illustrates the speed of approach for juvenile rats ($F = 1.36$; $p = 0.13$ ANOVA); the lower is for adults ($F = 49$; $p < 0.01$ ANOVA). **(F)** Whisker tip distance to target (d_w) in relation to body-to-target position. Left: Juvenile rats -- $r^2 = .52$, Nose distance effect: $F = 4.82$; $p<0.001$; Right: adult rats -- $r^2 = .47$, Nose distance effect: $F = 2.92$; $p<0.001$. **(G)** Most protracted angle at each whisk cycle in relation to the set point versus the nose distance d_n from target. Left: Juvenile rats -- Fit slope= 0.03 deg/mm, Nose distance effect: $F = 0.85$; $p=0.09$. Right: Adult rats (Fit slope= -0.17 deg/mm, Nose distance effect: $F = 1.59$; $p<0.01$). Black lines are the fit to the data, red lines are no correlation fit, i.e. the trend expected if the d_n and **α** were not correlated.

Adaptive frequency modulation develops postnatally and after P21. Whisking frequency distribution mostly lies between 5 and 20 Hz for both juvenile and young adult groups during stationary target localization, independent from the animals' location in respect to the target (Fig.2A). In juvenile animals tactile exploration does not change the whisking frequency (Fig.2B, top), although adult rats reduce frequency of whisking upon whisker contact (Fig.2B, bottom). Considering that protraction and retraction amplitudes are comparable across animals (Fig.2C), contact induced change in whisking frequency is likely to be mediated neuronally, by controlling the phasic regulation of whisking, for example by a delay line.

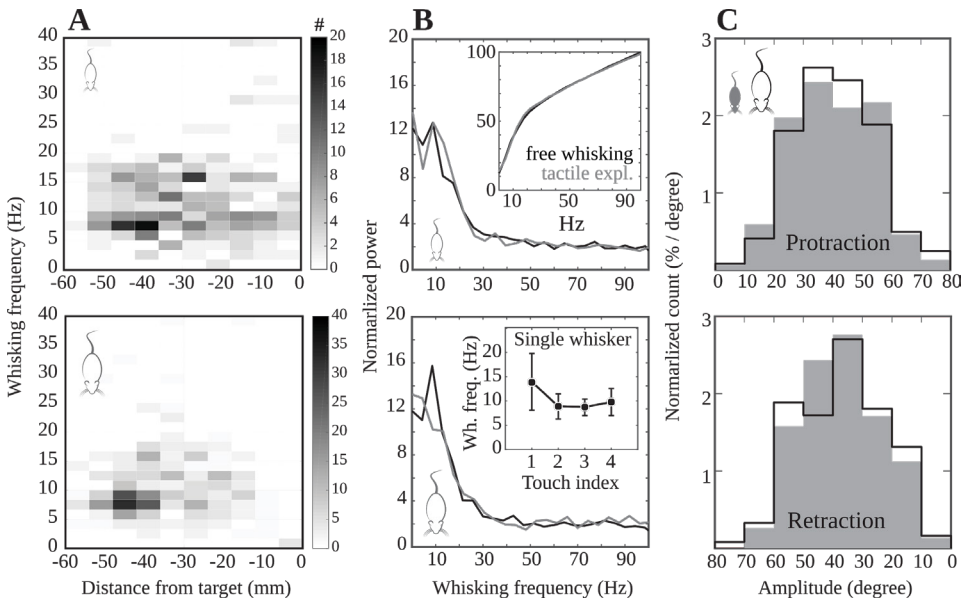

FIGURE 2. Frequency and amplitude modulation in juvenile and adult rats. (A) Histogram of whisking frequency binned (5 mm) in relation to the body-to-target distance (Top: Juveniles, F = 1.36; p =0.07 Two-way ANOVA; Bottom: Adults, F = 12; p=0.01; Two-way ANOVA). **(B)** Normalized power of frequency range in free whisking versus during tactile exploration. Top: Juvenile rats (whisking mode effect: F = 0.75; p=0.22, ANOVA); inset shows the cumulative frequency distributions (whisking mode effect: F = 0.57; p=0.79, ANOVA). Bottom: Adult rats (whisking mode effect: F = 13.83; p<0.01, ANOVA); inset: whisking frequency binned by touch (data from rats with single whisker, N= 5 rats; N=30 trials). (**C)** Normalized distribution of protraction and retraction angles in each whisk cycle (Top -- Protraction: developmental effect, F = 1.78; p=0.27, ANOVA. Bottom -- Retraction: developmental effect, F = 3.43; p=0.18, ANOVA).

Sensorimotor adaptation and sensory acquisition across development

In active sensing, motor control is systematically modulated to optimize sensory acquisition as animals (neural circuits) maximize the inflow of task-related sensory information (*27*, *28*) while minimizing energy consumption (*29*, *30*). In the previous sections, I studied the active motor control of this adaptive computation. In this section, I analytically investigate the development of sensory acquisition strategies.

Juvenile rats collect more sensory information prior to successful gap-crossing. Analysis of the tactile exploration duration showed that young adult rats spend significantly less time collecting sensory information compared to juvenile rats prior to successful object localization (Fig. 3A) although the duration of single touch event was statistically comparable between the two groups (Fig. 3B). Considering that the total exploration duration is higher in juvenile animals, although single touch events are comparable across juvenile and adults, the difference in sensory exploration is likely to be due to increased number of whisker contacts in the juvenile animals, which is supported by the experimental observations (Fig. 3C). Deconvolution of the contact duration with number of whiskers simultaneously in contact with the target showed that, in juvenile animals, contact duration increased when there were multiple whiskers palpating on the target (Fig. 3F).

Juvenile rats collect most of the sensory information closer to target, recruiting larger number of whiskers in comparison to adults. Juvenile and adult rats employ two different strategies to harvest sensory information. Adults make most of their contacts within 2-5 cm from target. In juveniles, likelihood of sensory exploration increased as the juvenile rats approached the target (Fig. 3D). Deconvolution of the number of simultaneous whisker contacts with the relative distance to the target (Fig. 3E) showed that juvenile rats gather most of the sensory information closer to target while keeping higher number of whiskers simultaneously in contact with target. Adults gather most of the sensory information further away from the target (2-4 cm) and with lesser number of whiskers simultaneously in contact at any given time (Fig.3E, right). Accordingly the duration of contact varied with relative distance to the target across groups (Fig.3H). In adult animals the contact duration remained constant (and brief) while they were within 2-5 cm of the target (Fig.3H). As they got closer to the target, the contact duration increased, probably because at this range they keep their whisker protracted, increasing the contact duration without regulating the whisk cycle (Fig.3H, right). Finally, the analysis of the approach speed showed that while juvenile animals approach the target with a relatively constant speed, adults increase their speed as they get closer to the target (Fig. 3I). Accordingly they spent relatively less time closer to the target (Fig. 3J).

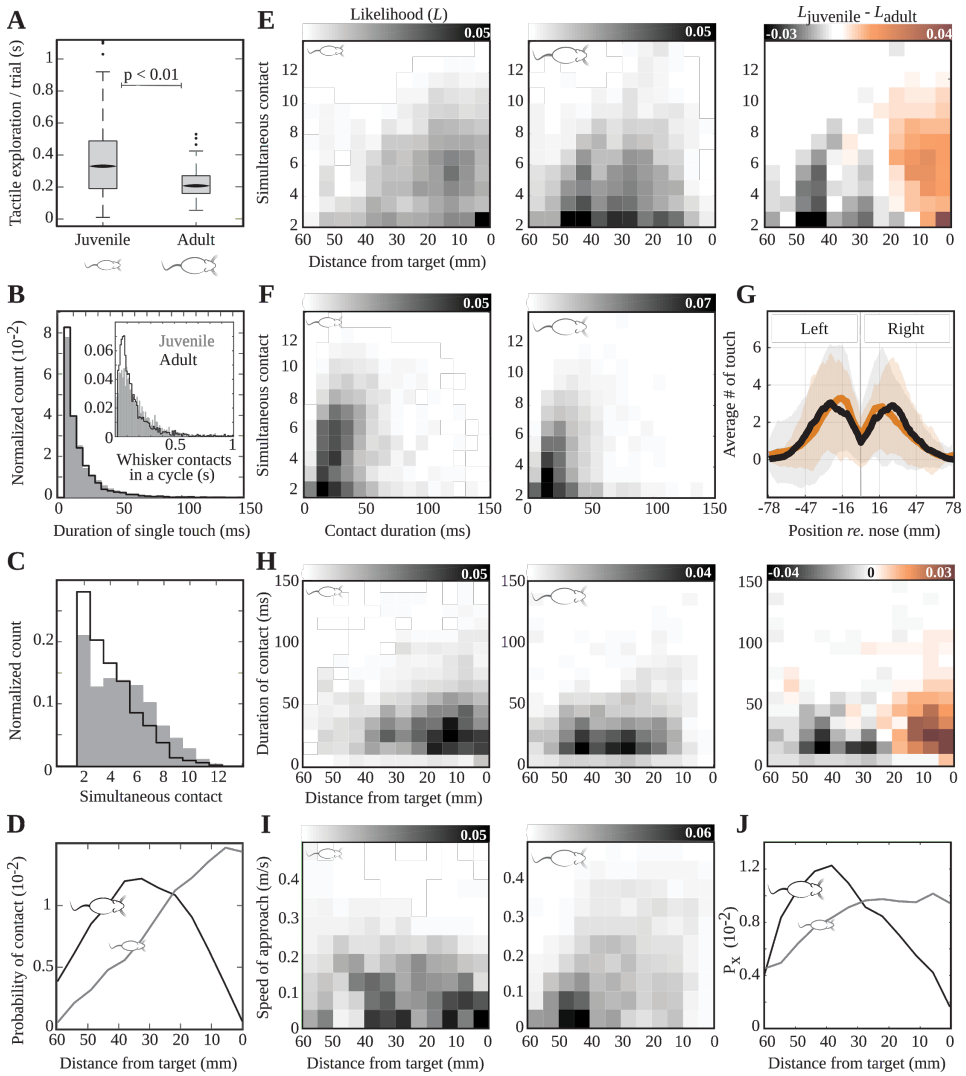

FIGURE 3. Statistics of whisker guided tactile exploration across development. (A) Adult animals spend significantly less time exploring the gap compared to juvenile rats prior to successful object localization (developmental effect: F = 87; p<0.01). **(B)** Normalized count of duration of single touch, Grey: juvenile, white: young adult (developmental effect: F = 0.74; p=0.49). The inner figure shows the total duration of contact within a whisk cycle across all the whiskers (developmental effect: F = 2.45; p=0.21). **(C)** Normalized count of the number of whiskers being simultaneously in contact (developmental effect: F = 27; p<0.01). **(D)** Spatial probability distribution of contacts (developmental effect: F =251; p<0.01). **(E)** Spatial distribution of likelihood of simultaneous number of contacts (developmental effect (observed variable distance): F =221; p<0.01). **(F)** Histograms of average contact duration grouped by the number of whiskers simultaneously in contact with the target (developmental effect (observed variable contact duration): F =73; p<0.01). **(G)** Normalized distribution of contacts in the horizontal plane (developmental effect: F =0.364; p =0.546). **(H)** Histograms of contact duration grouped by the relative distance to target (developmental effect (observed variable distance): F =198; p<0.01). **(I)** Distribution of speed of approach by relative distances to target (developmental effect (observed variable distance): F =369; p<0.01). **(J)** Normalized distribution of time spent in respect to relative distance to target (F =183; p<0.01). All statistical comparisons are made using (two-way) ANOVA.

An *in silico* model of active whisking

The results outlined above show that juvenile animals do not utilize the sensory information they acquire to adapt their whisking pattern. There are several plausible mechanisms how adaptive motor control can be implemented during active sensing. To systematically address these mechanisms, I have developed an *in silico* model of whisking. The whisking module of the model is based on a pair of coupled oscillators driving protraction and retraction, functionally mimicking the central pattern generators in the brainstem (*31*, *32*). As in the the biological circuits of sensorimotor control these oscillators receive top-down hierarchical input that could modulate whisk cycle (*31*, *32*). The model integrates body locomotion and whisking motor control, thus can decouple the two active motor control processes to address how adaptive changes in body positional control relate to adaptive whisking. Sensory feedback, e.g. duration of contact (tactile exploration), can be integrated to establish close-loop sensorimotor control.

Using this model, non-adaptive (uniform) whisking, as observed in juvenile animals, can be simulated by driving the oscillators as an open-loop, i.e. the whisk frequency, protraction and retraction onsets are not modulated by sensory information but intrinsically regulated (Fig.4C-E). The result is *in silico* whisking at a constant frequency independent from the exploration state, relative distance of the animal to the target or the history of tactile exploration -- all behaviorally shown in juvenile animals (Figs.1-3). Adult animal, on the other hand, perform adaptive whisking, systematically protract their whiskers further as they get closer to the target. *In silico* such a control system requires close-loop integration of sensory and motor circuits which is implemented through recursive increase in protraction angle and decrease in whisking amplitude upon emergence of novel sensory information. This implementation successfully replicates the observed properties of adaptive motor control in adult animals (Figs.1-3) as adaptive whisking in silico results in forward placement of the whiskers, increased whisker protraction amplitude, reduced amplitude and frequency of whisking (Fig.4C-E).

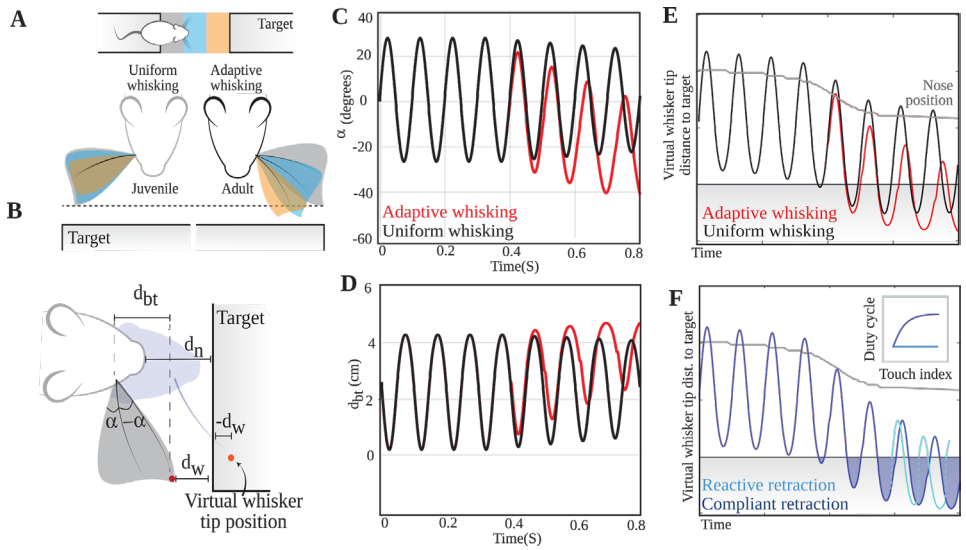

Figure 4. Whisking *in silico* (A) Uniform versus adaptive whisking as observed in juvenile and adult animals, respectively. Color code represents the relative distance to the target and the motor control phenotype at the corresponding distance. See Figures 1-3 for the behavioral data. Adaptive whisking is characterized by reduction in whisk amplitude, forward placement of whisker, increased protraction amplitude. During uniform whisking animals whisk at constant frequency and amplitude. **(B)** Sensorimotor variables of interest. Red dots denote the whisker tip (actual vs virtual); α is the angular displacement from the mid-point between the most retracted (i.e. retraction set-point, α) and protracted positions (protraction set-point, -α) of the whisker during whisking. d_n represents nose distance to target, d_w symbolizes the whisker's tip distance to target. d_w is negative when the virtual whisker passes through the target. d_{bt} is the distance between whisker's base on the snout and whisker's tip. **(C)** Angular displacement at the whisker base for adaptive whisking (red) versus uniform whisking (black). **(D)** Evolution of d_{bt} patterns during adaptive whisking (red) versus uniform whisking (black). **(E)** Whisker tip and body (nose) position in relation to target during a gap-crossing trial. **(F)** "Reactive" and "compliant" retraction as a part of adaptive sensorimotor control.

Next to this recursive adaptation, recent sensory information might regulate the whisk cycle to keep the duration of whisker contacts constant through "reactive retraction" of whiskers during close-loop control of sensorimotor control. Alternatively, if the sensory input does not have any influence on the retraction of whisking, the retraction would be compliant to the protraction thus as the animal gets closer to the object, the contact duration would be systematically increased (Fig.4F, inset). To experimentally address which of the two models of retraction is employed by animals, I have quantified the touch duration and duty cycle across consecutive touches (N=5 animals and 30 trials; Fig.5). The results showed that touch duration increases after the first contact, plausibly because the animals get closer to the target, after which it remains

constant (Fig.5A), although the duty cycle remains constant across all touch events (Fig.5B). These results suggest that the sensory information is used for both creation of a close-loop sensorimotor control that modulates the amplitude of whisking, but also for enabling "reactive retraction" to ensure constancy of whisker contact duration across touches.

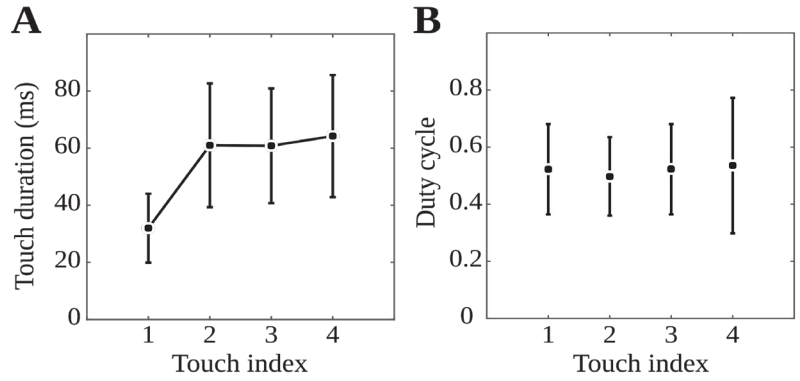

FIGURE 5. Animals actively control the contact duration and duty cycle. Data from animals with single whisker (unilateral C2; N=5 animals and 30 trials). **(A)** Touch duration as a function of touch index. Note that after the first contact, the contact duration is stabilized. **(B)** The duty cycle of whisking, i.e. duration of contact in respect to the duration of a whisk, across the different touch events.

To validate our *in silico* model of whisking, I performed simulations with behavioral variables observed in juvenile and adults animals which successfully created uniform and adaptive whisking *in silico* (compare Fig.6A-B to Fig1.F-G).

This model provides a valuable platform to study the contribution of different whisking attributes to sensory information acquisition. Figure 6 C-F compare the contact durations between the adaptive sensorimotor scenario with non-adaptive whisker control. Contact durations are shown in each figure for five consecutive touches during object localization task (see Fig. 6C). The simulation provides means to decouple each motor control variable study their effect on sensory information individually. The body locomotion strategies are the same across the first three experiments (Fig.6 C-E) and similar to nose distance to target shown in Figure 4E. In these sets of experiment the reactive retraction is disabled to observe solely the effect of adaptive motor control on touch duration. In Figure 6C, the effect of sensory driven adaptive gradual increase of mid-point is studied.

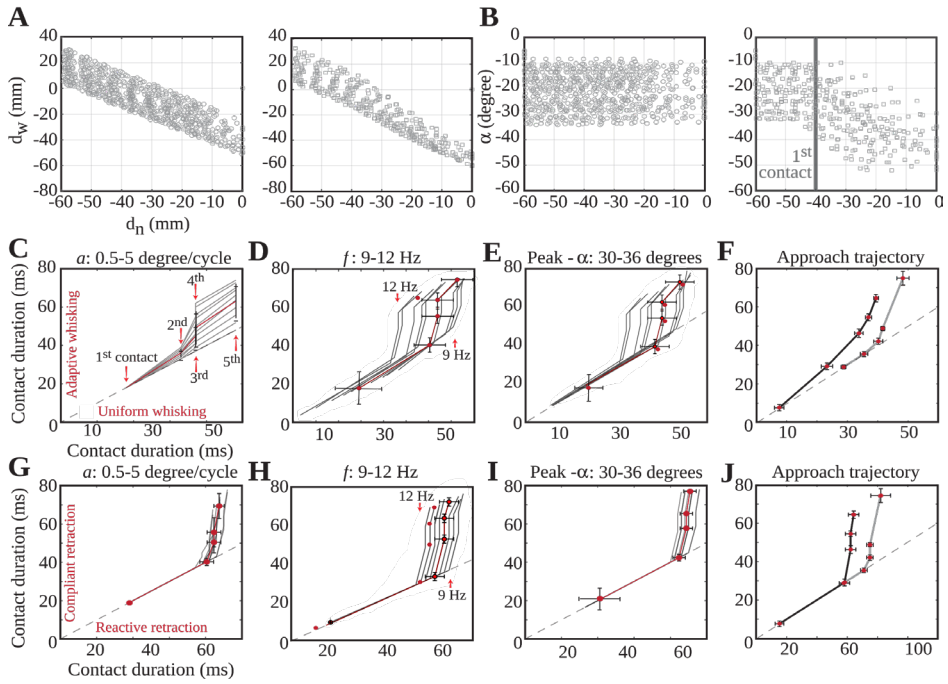

FIGURE 6. Simulated whisking *in silico*. (A) Simulated tip distance to target d_w in relation to body-to-target position. Left: uniform whisking, right: adaptive whisking. **(B)** Adaptive motor control of whisker angular protraction. Left: uniform whisking, right: adaptive whisking. **C)** Contact duration in adaptive versus uniform whisking. Sensory driven adaptive gradual increase of mid-point increases the contact duration. Touch sequences are as shown in the figurine. The dashed line shows the result for uniform whisking with zero mid-line adaptation. **(D)** Contact duration in adaptive versus uniform whisking. Increasing the frequency decreases the contact duration. **(E)** Contact duration in adaptive versus uniform whisking. Increasing the maximum protracted angle increases the contact duration. **(F)** Contact duration in adaptive versus uniform whisking. Approach (gray) pattern entrained by juvenile rats results in higher contact duration. **(G)** Contact duration in compliant versus reactive retraction (investigating the effect of rate of mid-point adaptation). **(H)** Contact duration in compliant versus reactive retraction (effect of whisking frequency). **(I)** Contact duration in compliant versus reactive retraction (effect of maximum protraction angle). **(J)** Contact duration in compliant versus reactive retraction (effect of approach trajectory, juvenile (gray) versus adult (black)).

As mid-line adaptation gradually increases from 0.5 to 5 degree per cycle (touch) animal pushes the whisker further towards the object which in lack of adaptive controls for retraction and adjusting the touch duration results in longer touch durations. On the other hand, in uniform whisking touch duration is only a function of nose distance to target and frequency of whisking, for instance it is evident that in the third and fourth touch contact duration is identical in uniform whisking. Figure 6D studies the

effect of whisking frequency on touch duration. Whisking frequency directly gauges contact duration.

One of the parameters in this model is the maximum whisking retraction and protraction angle. Figure 6E shows the result of changing maximum protraction angle on touch duration. The locomotive strategies (speed of approach) of juvenile and adult rats in relation to time and space was studied in the earlier sections and shown in Figures 1 and 3. Adults approach the target slowly prior to acquisition of the early sensory information but then maneuver quickly to the target platform, while the Juvenile group approach the target with a uniform speed. In Figure 6F, the effect of these locomotive strategies on touch duration is shown.

Figures 6 G-J compare the contact duration between compliant retraction and reactive retraction. Note that second to fifth touch durations are not asymptotic (unlike the behavioral observations, Fig.5) because the model predicts the retraction time based on the sensory information in the previous cycle and reference motor copy of the current whisk cycle. Thus, body dispositions during the current whisk cycles, and their effect on touch duration are not included but could be integrated as an error term. And finally, Figure 6G-J show the role of mid-point adaptation, frequency variation, maximum protraction angle and approach trajectory on contact duration for compliant retraction and reactive retraction.

DISCUSSION

In whisking, similar to other active sensing paradigms, sensory information alone is not sufficient to form a percept of external world. This percept hinges on the interplay between motor controls and sensory information. The sensory information coming from whiskers, together with the spatial position of the whisker at the time of contact contains the necessary information required for object localization. Here, using high-speed infrared videography, I studied rats locating a stationary tactile target in two life stages juvenile (P21) and adults (~P65). I simultaneously quantified the sensory input, the whisking motion and body locomotion. This is the first study which addresses development of whisker-based navigational adaptive sensorimotor control in rats.

Early postnatal development of the somatosensory cortex

For my experiments in juveniles I focused on P21 primarily because, at this age, the whisker system of the rats is believed to be functionally (see introduction) and ana-

tomically mature. The barrels begin to emerge at E9 (prenatal) and continue to form characteristics of its mature network until (P21) postnatal (*14*). Patterning and plasticity of the barrel cortex, the targeting of ventrobasal thalamic axons, the formation and functional maturation of synapses during the initial critical developmental periods are extensively investigated (*8–11*). Initially, through corticogenesis, the intrinsic genetic programs determine cortical arealization. Thereafter, thalamocortical axons innervate the cortical plate (*33*, *34*). Then, barrels start to form around P3 and matures by P7 (*35*, *36*). Around P14, TCA projections innervate the barrel cortex (*37*) and central pattern generators in the brainstem start controlling whisker motion (*13*). In the third postnatal week, the pattern of GABA immunoreactivity, the receptive field of excitatory neurons and their axodendritic projections reaches maturity (*37*, *38*). This is the time that the barrel cortical neurons are considered to be mature (*14*). Considering that both body positional control and the whisker motion mature during this period (see introduction), this age group is the earliest time course that one can address the question when the adaptive control of whisker position matures.

Juvenile rats do not utilize sensory information for motor control: Open-loop whisking

I found that goal-directed body locomotion and whisking both are controlled processes independent from the developmental age however adaptive whisking matures later after P21 (Fig. 1). Juvenile rats navigate towards target with uniform speed while young adults body locomotion changes based on the relative distance to the target. The experiments showed that adults increase their protraction angle as they approach the target (driven by touch), and this adaptation happens through advancing the mid-point around which the whisker swings at each cycle, while juvenile rats whisk uniformly the entire exploration period.

Sensory information modulates whisking frequency as a part of the adaptive sensorimotor control and this modulation develop after P21 (Fig. 2). Adults whisk with lower frequencies during tactile exploration in comparison with free whisking mode, while sensory information does not modulate whisking frequency in juvenile group. In contrary to our results Berg and Kleinfeld (*26*) reported increased whisking frequency when rats change their whisking mode from ‘exploratory’ (range 5–15 Hz) to ‘foveal’ whisking (15–25 Hz) in search for reward. In their experiment female Long-Evans rats were trained to whisk in search of a food reward, while in this chapter male wistar rats were trained to perform spontaneous gap-crossing task. More importantly, our results are specifically looking at touch induced changes in sampling frequency, although the previous results were limited to free-whisking and search behaviors. Therefore I

suggest that in addition to exploratory and foveal whisking, there is another mode of active whisking regulated by contact.

Experiments also showed that juvenile rats collect more sensory information prior to successful object localization. They make most of the contacts closer to target, with higher number of whiskers simultaneously in contact, and these contacts are longer in duration (Fig. 3). This exploratory pattern could be explained by body locomotion; adults position themselves away from the target during the exploration, while juvenile rats spend most of this time closer to target.

Function of adaptive whisking

During active sensing, adaptive sensorimotor computations aim to optimize the sensory information acquisition to maximize the task-related sensory information and minimize the energy consumption (*29*, *30*). When rats palpate onto the target platform during gap-crossing task with multiple whiskers, they collect redundant information (*18*): platform´s edge structure is uniform and its elevation along the edge is constant, thus information available across different whiskers in contact are redundant. One of the principal functions of this adaptive whisking could be to compensate for the redundant sensory information, as our results demonstrate that in adaptive whisking strategy less number of whiskers are simultaneously in contact. Reduced redundancy is proposed to increase the channel capacity and increase the speed of information processing (*39*, *40*). Moreover, the simultaneous touches are shown to integrate sublinearly and add minimal information at the network level (*41–43*). Thus an outcome of this adaptive sensorimotor computation could be to optimize sensory acquisition by avoiding making contact with excessive number of whiskers simultaneously which add minimal information. Besides reducing redundancy, adaptive motor control governs pattern of whisker movement, which dictates the sensory signal transmitted along each whisker and the exploratory field of each whisker. This, could potentially influence the sensory information available to brain to solve the control task.

I found that whisker retraction is actively controlled to keep the whisking duty-cycle constant (Fig. 5). I observed that touch duration increases from first touch to the second, and there on the duration of touch stays constant. These results are in agreement with the reduction in the frequency of contact after the first touch (Fig.2). In addition, the data indicates that rats keep the duty cycle constant during the navigation task. Together, the results propose an active mechanism for controlling the whisker retraction to keep the touch duration and its duty cycle constant in a whisk cycle. Body locomotion changes body to target distance between each whisk cycle, the-

refore a reactive mechanism to retract the whiskers based on the received sensory information is necessary to control touch duration and duty cycle.

OUTLOOK

In object localization, rats iteratively integrate sensory information by modulating their whisker parameters to optimize the sensorimotor computation. Sensorimotor systems utilize probabilistic models to predict unobserved variables (*44*). Brain generates prior hypothesis based on its internal models of external world, and combines them with acquired sensory information to form a posteriori hypothesis of target location (*45*). As the animal approaches the target in gap-crossing task, acquired sensory information in egocentric coordinates, modulate the posteriori hypothesis. Using learned forward models these hypothesis translates into motor action and generate adaptive sensing. One hypothesis proposes that updating the internal models could result in learning these forward models using the sensory error signals to learn the inverse models (*46*). Our results suggest that learning these forward models, which their development is activity dependent, potentially happen after P21.

Taken together, our results indicate that although juvenile rats are capable of successful object localization and navigation, their adaptive sensorimotor strategy matures only in later stages of life. Considering the results from whisking *in silico* suggest that encoding of the touch duration and adaptive control of whisker position could potentially explain the development of adaptive motor control, chronic recordings from S1 and M1 performed during the last week of the first postnatal month could shed light onto the developmental (including experience-dependent) and neuronal mechanisms of sensorimotor computation.

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4

Serotonergic regulation of adaptive motor control

Active sensing requires adaptive motor (positional) control of sensory organs based on contextual, sensory and task requirements. In Chapter 3, I have shown that adaptive motor control for whisker based exploration develops postnatally after the maturation of intracortical circuits. Altering sensorimotor network connectivity during this period is likely to shape sensorimotor computation also in adulthood. Serotonin is among the cardinal developmental regulators of network formation, thus changing the serotonergic drive might potently control the emergence and maturation of sensorimotor computation. Here I tested this hypothesis on an object localization task by quantifying the motor control dynamics of whiskers during active sensing. The results showed that sustained alterations of the serotonergic signaling in serotonin transporter knockout rats, or the transient inactivation of the transporter during early postnatal development, impairs the emergence of adaptive motor control of whisker position based on recent sensory information. A direct outcome of this altered motor control is that the mechanical force transmitted to whisker follicles upon contact is reduced, suggesting that increased hyperexcitability observed after altered serotonergic signaling is not due to increased synaptic drive originating from the periphery upon whisker contact. Graph based neural circuit simulations showed that these observations can be explained by a heuristic network model of sensorimotor computation which links the change in feed-forward excitatory drive propagating from the sensory periphery to reduced synaptic inhibition in the central nervous system. These results argue that postnatal development of adaptive motor control requires intact serotonergic signaling, and that even its transient dysregulation during early development causes long-term sensorimotor disturbances in the adulthood.

INTRODUCTION

During active sensing the position of sensory organs is adaptively controlled based on sensory and contextual information as well as learned task requirements (*1–3*). In the whisker system, for example, the pattern of whisking during object localization is modulated by whisker touch as animals protract their whiskers towards the presumed tactile target location (*4*). Modulation of motor (whisking) pattern by sensory input allows compensation for the change in body position in respect to the target (*5–7*). A recent study, see Chapter 3, showed that this adaptive motor control develops postnatally after the 4th postnatal week, but developmental mechanisms of adaptive sensorimotor control are yet to be unraveled.

Postnatal development of sensorimotor circuits relies on the combination of intrinsic molecular cues and neuronal activity that is coherent across population of neurons; while intrinsic cues ensure orderly development of the sensorimotor circuits, activity-dependent processes fine-tune the circuits thereafter (*8–12*). Emerging evidence suggests that neuromodulator neurotransmitters, in particular serotonin (*13*), powerfully regulate the development of sensorimotor circuits. Altered serotonergic signaling during early postnatal development impairs the structure and function of neural circuits (*14–19*), results in anxiety and depression like behavior (*14*, *19*, *20*) and hinders goal directed navigation and object recognition (*14*, *19*). Increasing extracellular serotonin availability during development impairs sensorimotor behavior well into adolescence (*19*) while administration of select SSRIs (e.g. Fluoxetine, Sertraline, citalopram) during a critical period causes delayed development of several reflexes and muscle strength (*18*, *21*, *22*) as well as sensorimotor coordination (*23–25*) and motor exploration (*26*, *27*), (*28*). These findings argue that changes in the serotonergic drive early in life might be critically involved with the maturation of sensory and motor circuits.

In agreement with these observations, we previously showed that serotonin transporter knockout (Sert-/-) rats display behavioral and neuronal sensory hyperexcitability (*27*) in the whisker system. At the functional level a major consequence of network excitability is the faster integration of sensory information during whisker based tactile navigation (*27*). Because the barrel cortex and the primary motor cortex have reciprocal monosynaptic communication, altered serotonergic signaling could potentially dysregulate whisker positional control during sensory navigation. Here I addressed this question using publically available high-speed videography database of rats performing a tactile object localization task, introduced in Chapter 2. Quantitatively analyzing the motor control of whisker and body position, I show that sustained alterations

of serotonergic signaling in serotonin transporter knockout rats, or the transient inactivation of the transporter during early postnatal development, impairs emergence of adaptive motor control of whisker, but not the body positioning in the adulthood. Simulation of the mechanics of the whisker displacement showed that the absence of goal-oriented adaptive whisking reduces the mechanical forces at the whisker follicle. These results argue that previously described sensory hyperexcitability upon altered serotonergic signaling (*27*) is not due to increased mechanosensory drive, and that hyperexcitability originates in the central nervous system. In short, postnatal development of adaptive motor control requires intact serotonergic signaling, and that even transient changes in serotonergic signalling during development cause long-term sensorimotor disturbances in the adulthood, impairing close-loop sensorimotor control of whisker position, reducing the precision in motor control during goal-directed navigation, and reducing touch induced force transmitted to the whisker follicles.

MATERIALS AND METHODS

The experiments in this chapter were performed using 38 male wistar rats as described in Chapter 2. In short, animals shuttled between two elevated platforms with a variable gap-distance in between them as they searched for a tactile target in their immediate environment in the absence of any visible light. Animal behavior on this so-called spontaneous gap crossing task (*1*, *4*, *29*) was recorded by a robotic high-speed camera using infrared back-lights. Videos were analyzed using custom written routines in Matlab to extract whisking and body locomotion dynamics at a sampling resolution of 5 ms.

Animals

Animals were randomly assigned to two groups: Half of the rats were genetically modified (N=14) or pharmacologically treated (N=5) to alter serotonergic neurotransmission. Serotonin transporter knockout rats (Slc6a41Hubr, N=14) were originally generated on a Wistar background by N-ethyl-N-nitrosurea (ENU)-induced mutagenesis (*30*). To transiently interfere with the serotonergic signalling after birth, fluoxetine hydrochloride (10 mg/kg/day, Sigma Aldrich), a selective serotonin reuptake inhibitor, was dissolved in water and administered orally to wild type Wistar rats (N=5) for 7 days after P1. The other half of the rats were wild type (N=14) and vehicle (tap water) controls (N=5).

Analysis of tactile exploration statistics

All recorded images were analyzed off-line in Matlab. A background image, acquired before the subject's entrance to the field of view, was subtracted from all other frames to aid with moving object detection. This background image was also used to identify the stationary tactile target, i.e. the elevated platform animals are searching for, by finding the transition point from low to high brightness in the illumination.

For the analysis of the head (body) and whisker position, the head contour was extracted using a standard contrast based edge detection approach. The positions of ears and nose were used to triangulate the head direction. Angular deviation of the nose from head center plane (between the ears) allowed calculation of the head angle in respect to the tactile target and the relative nose distance to target. Whiskers (N=6 whiskers/trial, N=3 whiskers/snout) were tracked manually. Whisker contacts with the target were marked manually for all whiskers. Animals had all of their whiskers intact throughout the experiments. Angular displacement of the whisker base in respect to target was computed for each tracked whisker. Only data from whisker distances (gap distance >14.5 cm), where animals collected tactile information from the target using solely their whiskers prior to decision-making, were analyzed. Thus tactile exploration using the touch receptors embedded in the skin (as it invariably happens at short (nose) distances (*29*)) do not interfere with the sensorimotor behavior (*29*) and the adaptive sensorimotor control of whisker position during tactile navigation (*1*, *4*).

Whisker position in respect to the target platform was calculated as described previously (*1*, *4*). Angular protraction of the whisker was quantified at the whisker base, in respect to the position of the whisker at rest, i.e. the mid-point between the protraction and retraction set-points in a whisk cycle (Figure 1A). Whisker tip position and relative position of the tip of the nose in respect to the tactile target were extracted using custom routines. Absolute distance between the two platforms was defined as the target distance (in respect to the home platform).

Mechanical modeling of whisker bending

Whiskers can be modeled as a flexible beam that transmits mechanical information to mechanoreceptors in the follicle. Whisker geometry, density and its elastic moduli govern the mechanical information at the follicle. This mechanical "simplicity" allows mathematical approximation of the tactile (mechanical) inputs transmitted by the vibrissae during active tactile exploration.

Whisker shape can be approximated by a quadratic fit (a parabola) (*31*). Given that the density of the keratinized tissue diminishes almost linearly from base to tip (*32*, *33*), whisker's elastic moduli govern its bending stiffness. The two most relevant moduli

to whisker mechanics are the Young's modulus (E) and shear modulus (G). Young's modulus is essential to model the whisker in 2D, as shear modulus is significant only when a force is applied to the whisker surface while the opposite site of the whisker is held constant by another equal force. Equation below translates the curvature (k) at each point (s) along the whisker to bending moment (M), given the stiffness of the whisker at each point. This bending moment (the product of stiffness and the curvature), is used to estimate the signals that rats experience during whisker deflection (*34–38*).

$$\Delta M(s) = (stiffness)\Delta\kappa(s)$$

Whisker contact induced mechanical information at the whisker follicle can be approximated by calculating the bending moment (M), the axial force (F_x) which is the force directed along the length of the whisker near the base, and the transverse force (F_y) that is perpendicular to the axial force (Fig.4A) as described previously (*34*).

To analytically quantify the sensory consequences of adaptive motor control, I simulated the force transfer along the whiskers during active sensing across the four groups using elastica 2D in MATLAB (*34*, *36*). The body locomotion towards the object is modeled by coordinating the contact point of the whisker to the target. Body-to-target position together with egocentric whisker position (alpha of the parabola fit to the whisker) govern the location on whisker that contacts the object (the location on whisker that bending force applies).

RESULTS

Serotonergic signalling is critically involved in development and maturation of sensorimotor circuits however whether serotonin contributes to the emergence of close-loop sensorimotor computations for adaptive motor control is unknown. Here, I studied genetically engineered or pharmacologically treated rats exploring a tactile target to address this question.

Task performance and development of goal-oriented motor control strategies

During goal-oriented navigation, sensorimotor transformations require integration of information in self- (egocentric) and world-centric (allocentric) coordinates. Sensory circuits represent the world in egocentric coordinates but body motion and moving appendages (e.g. whiskers, limbs and head) necessitate discounting the changes in

body position for integration of sensory information in space and time. In the adult whisker system this is achieved by adapting whisker protraction angle to the change in body position in respect to tactile target to perform a form of vector computation where whiskers and body are treated as coupled manifolds (*1*). This computation is learned after the first postnatal month (see Chapter 3), upon sequential emergence of motor control of body and whiskers (*39*). If serotonergic signalling is required for the adaptive sensorimotor computation, body or whisker motion control might be impaired by altered serotonergic signalling during development.

To observe the motor control dynamics during or following altered serotonergic signalling, four groups of rats were studied on the gap-crossing task (*1*, *4*, *27*, *29*, *40*, *41*) : Serotonin transporter knock-out (SERT-/-, N=14) had constitutive deletion of the transporter, while transient pharmacological inactivation of the transporter during development (N=5) allowed the assessment of serotonergic contribution to the emergence of sensorimotor control. Wild-type controls (SERT+/+, N=14) and vehicle treated groups (Vehicle, N=5) served as controls.

All groups successfully acquired the task. Animals increased the maximum gap-distance at which they successfully located the tactile target by four-folds over the course of 10 training sessions (Figure 1B). In every session animals were tested at multiple gap-distances (range: 3-18 cm), each constituting a trial. After the completion of a trial, gap-distance was randomly selected from a normal distribution where the distribution mean increased and the variance is reduced with increased number of training sessions completed on the task (*27*).

All groups employed a similar locomotive motor strategy to accomplish the task. Animals approached the target at a comparable rate (Fig. 1C) and speed (Fig. 1D). Despite the similarity in their approach to the target, animals that received transient (with Fluoxetine injections) or chronic (SERT-/-) intervention with serotonergic signalling made significantly less number of contacts with the target during the last phase of the approach (i.e last 29 mm; Figure 1E, 1F) as previously shown in adult SERT -/- animals (*27*). Since serotonergic intervention does not change animals' basic locomotion strategies, the reduction in sensory exploration might be due to distinct whisking strategies employed by the different groups of animals.

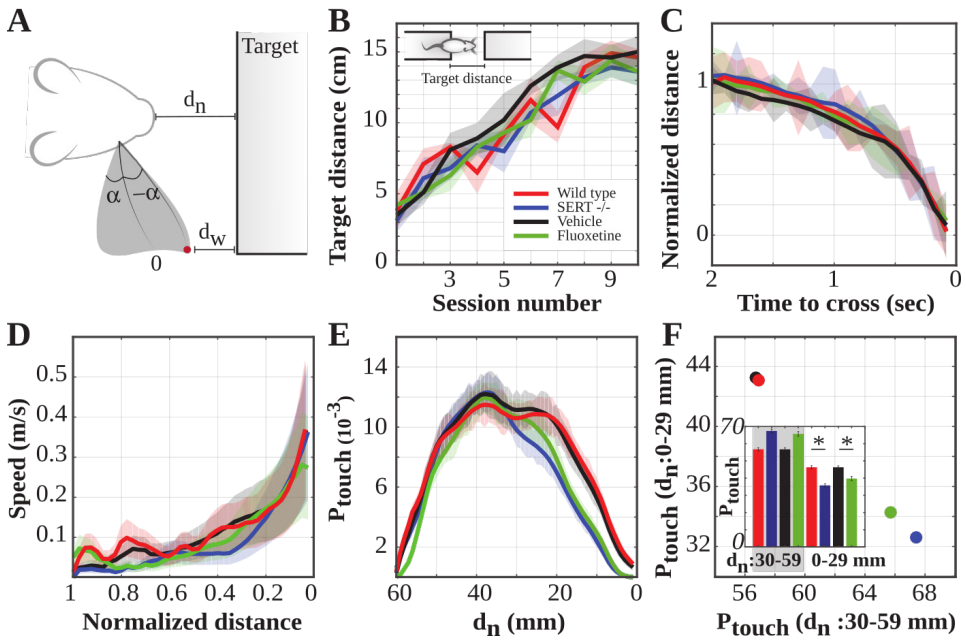

FIGURE 1. The role of serotonin in goal-directed sensorimotor navigation. (A) Behavioral parameters of interest. Red dot denotes the whisker tip; α is the angular displacement from the mid-point between the most retracted (i.e. retraction set-point, α) and protracted positions (protraction set-point, -α) of the whisker during whisking. d_n is the relative nose distance to target and d_w symbolizes the whisker's tip distance to target. **(B)** Learning curves for the four groups (Group effect: F = 1.83; p =0.141, 2-way ANOVA with df=3). **(C)** Normalized distance from target during the last 2 seconds of the exploration task (Group effect: F = 0.835; p=0.475, 2-way ANOVA with df =3). Note that average tactile exploration duration was less than a second. **(D)** Speed of locomotion during the last one second of the object localization task (Group effect: F = 0.670; p=0.517, 2-way ANOVA with df =3). **(E)** Normalized probability of contact with the target platform as a function of the relative distance to the target (Group effect: F = 22.931; p <0.001, 2-way ANOVA with df =3). **(F)** Normalized probability of touch based on the relative position of the animal to the target. Animals with altered transient (fluoxetine) and sustained (SERT-/-) serotonergic signalling required less number of contacts with the target platforms prior to successful object localization (Vehicle vs Fluoxetine, p<0.05; Wild type vs SERT, p<0.05; t-test). Data is presented as mean and the standard deviation from the mean, unless stated otherwise.

Adaptive sensorimotor control of whisker position

During tactile exploration of stationary objects animals protract their whiskers to the position in space where they recall as the location of the tactile target (*1*). In agreement with these observations, we found that as animals approached a stationary target, the relative distance between the target and their whisker tip position was reduced independent from whether animals received acute or chronic intervention with serotonergic signalling (Fig. 2A).

The adaptive control of whisker position is a function of the coupling between two moving manifolds, i.e. body movement and whisker motion. It was suggested that the functional contribution of the adaptive changes in whisker protraction might be to account for the changes in body position (*1*). If the brain were to perform vector computation to calculate the relative distance of the target by considering the displacement of the body and the whisker position, reduction of the protraction angle would allow to minimize the error in stimulus location estimates. The observation that for all groups whisker's tip position converges to the expected target position (Fig. 2A), however, does not imply that animals adaptively control the whisker protraction as the whisker tip position is also a product of the body position across whisk cycles. Therefore, I next quantified the change in whisker protraction as animals approached to target.

As it was shown previously (*1*, *4*) and confirmed in Chapter 3, the animals utilize adaptive sensorimotor control by increasing the maximum whisker protraction angle while decreasing whisking amplitude as they get closer to target. This protraction angle maximization is mediated through advancing the mid-point around which the whisker swings at each cycle. Groups with the modified serotonergic systems lack adaptive sensorimotor computation in respect to their corresponding control groups (Fig. 2B). This result argue that serotonergic signalling is required for maturation and execution of adaptive control of whisker position during development.

For tactile localization of stationary objects, animals integrate sensory information across the last ~3 whisk cycles as they use this "prior" to control whisker position (*1*). The progressive adaptation of the whisker protraction angle upon successive contacts with the target (Fig. 2C) indicate that wild-type and vehicle groups perform motor planning based on the recent sensory information. By integrating the sensory knowledge iteratively by the third touch, they increase the protraction angle, extend their whiskers towards the target (Fig. 2D). In SERT-/- and fluoxetine groups, however, whisker protraction angle was independent from the prior whisker contacts, and the relative location of the target. Because fluoxetine animals received the pharmacological intervention for a brief period of time during early postnatal development and they were behaviorally tested in the adulthood, these results also show that transient changes in serotonergic signaling during development have long lasting consequences for motor control in the adulthood.

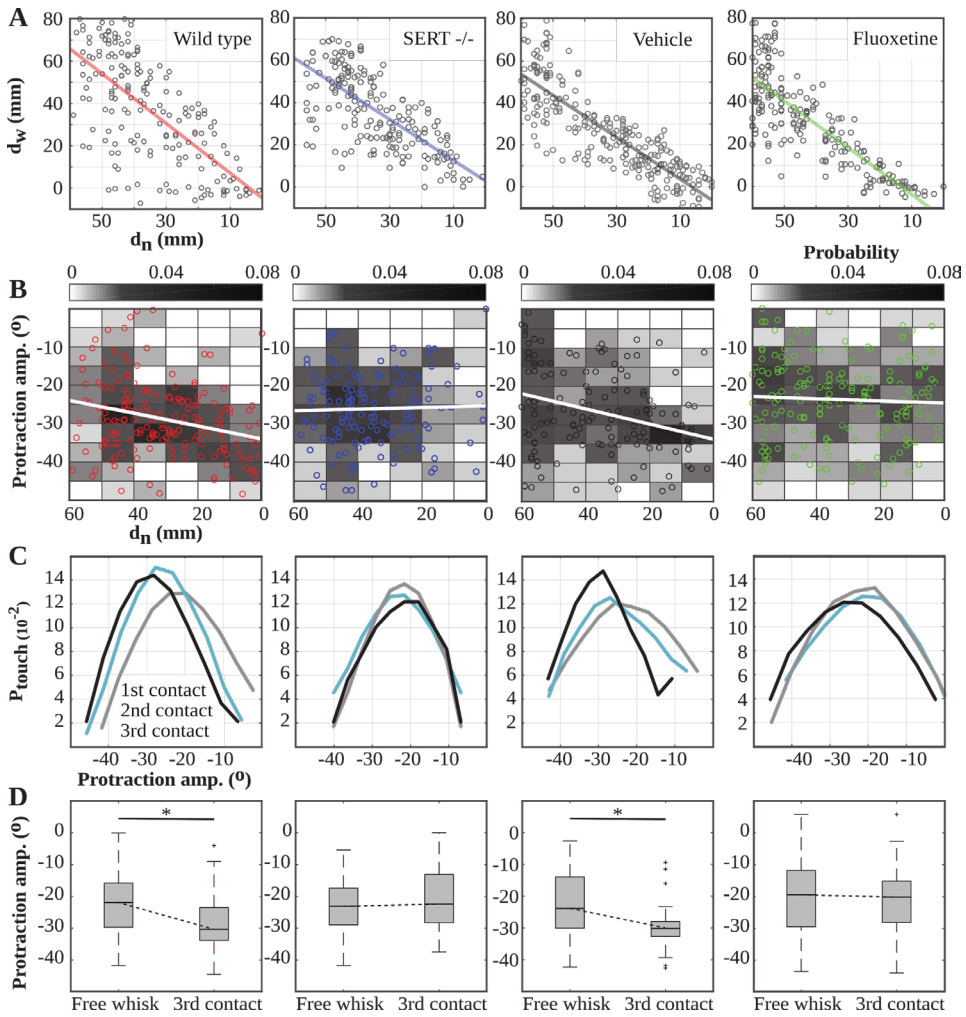

FIGURE 2. Serotonergic regulation of adaptive sensorimotor control of whisker protraction. (A) Whisker tip distance to target d_w in respect to the relative distance to target. From left to right: Wild-type (r^2 = .47, Nose distance effect: F = 2.92; p<0.001), Serotonin knockout (r^2 = .50, Nose distance effect: F = 5.42; p<0.001), vehicle (r^2 = .75, Nose distance effect: F = 9.29; p<0.001) and fluoxetine (r^2 = .72, Nose distance effect: F =7.58; p<0.001). **(B)** Most protracted angle at each whisk cycle in respect to the relative distance to target. From left to right Wild-type (Fit slope: -0.17 deg/mm, Nose distance effect (ANOVA): F = 10.59; p<0.01), Serotonin knockout (Fit slope: 0.02 deg/mm, F = 0.925; p=0.061), vehicle (Fit slope: -0.22 deg/mm, F = 47.46; p<0.01) and fluoxetine (Fit slope: 0.02 deg/mm, F =1.649; p=0.017). The 2D histogram of the data is represented at the background and a representative sample data is plotted on top. **(C)** Normalized histograms of protraction angles binned across consecutive whisker contacts with the target (Touch sequence effect (2-way ANOVA) -- Wild-type: F = 16.84, p<0.001 with df =2; Knock-out: F = 1.46, p=0.098 with df =2; vehicle: F = 7.98; p<0.001, df =2, Fluoxetine: F = 2.99, p=0.053 df =2). Light grey, light blue and black, represent the protraction angles related to the first, second and third contacts, respectively. **(D)** Change in whisker protraction angle between free-whisking and the third whisker contact with target (ANOVA, Wild-type touch sequence effect: F = 10.126; p<0.001 with df =1, Knock-out: F = 2.13; p=0.147 with df =1, vehicle: F = 26.369; p<0.001 with df =1, Fluoxetine: F = 1.55; p=0.214 with df =1).

Mechanical forces transmitted to the whisker follicle upon whisker contacts are reduced upon serotonergic dysregulation. Whiskers are specialized sensory hairs as such they do not contain any sensory receptors along their shanks; the mechanical displacement of the whisker is transmitted to the whisker follicle for sensory transduction. During non-adaptive whisking (as observed in SERT-/- and fluoxetine animals) the changes in follicle displacement upon whisker contact is solely due to change in body position (e.g. distance, head angle) in respect to the target. During adaptive whisking (as performed by wild type and control animals), the changes in whisking pattern also contribute to the mechanical forces at the follicle. Thus the quantification of the force in the follicle across non-adaptive and adaptive whisking could help to unravel the sensory contribution of adaptive motor control.

To quantify the force that arrive at the whisker follicle I implemented a mechanical model of the rat whisker (see Methods for details). I simulated whisker displacement during active palpation onto a stationary target as animals gradually approached to target based on the experimental data. In all *in silico* experiments only the last 3 cm of the approach was simulated where animals with serotonergic dysregulation contact target less often than their counterparts in the control groups (Fig.1E-F). For the simulation of non-adaptive whisking, the maximum protraction angle of the whisker was kept constant (~ 27°). During adaptive whisking the protraction angle gradually increased from 27° to 37° along the locomotion path as per experimental observations (Fig.2). The results showed that mechanical forces transmitted to the whisker follicle upon whisker contact is increased as the animal approached the target (see red traces, Fig.3) due to the reduction in the relative distance between the target and the body. Lack of adaptive whisking resulted in systematic reduction of the force transmitted to the whisker along three axis (blue traces, Fig.3). These results argue that adaptive whisking increases the force transmitted to the whisker base, increasing the feed-forward excitatory drive upon whisker contact. Lack of adaptive whisking after fluoxetine treatment or in the SERT-/- reduces forces in the whisker base upon whisker contact, thus reducing the sensory information originating from the periphery.

A network model of adaptive whisking

Sensory exploration and motor control are coupled processes. Considering that lack of adaptive whisking reduces mechanical forces traveling along whiskers upon whisker touch (Fig.3), this change in the sensory drive could potentially alter the motor control of whisker position in subsequent whisk cycles. To address this question, without the confounding variables (including compensatory change in body position) of navigation in freely behaving animals, I built a graph based network model of whisking.

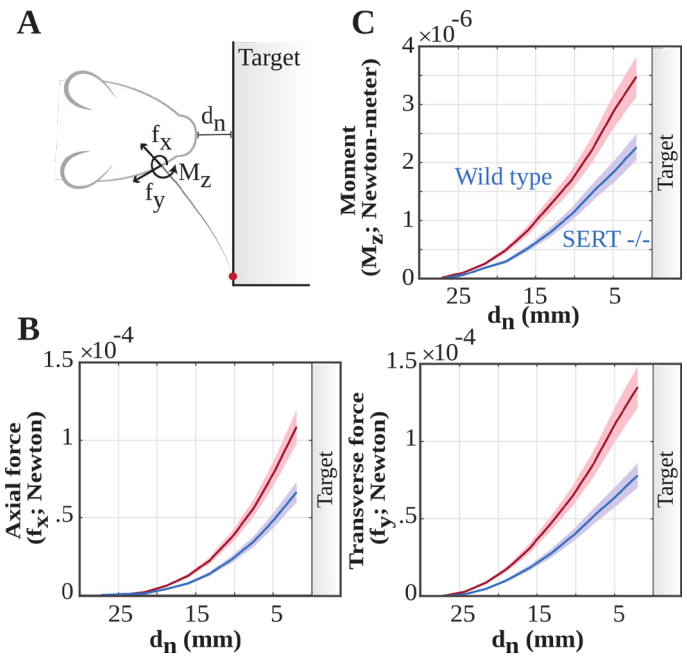

FIGURE 3. Lack of adaptive sensorimotor control upon altered serotonergic signaling reduces the force transmitted along the whisker upon contact with a tactile target. (A) Whisker contacts with objects in the plane of whisking change the axial force (F_x), transverse force (F_y) and the reaction moment (M_z) at the whisker base, and leads to mechanoreceptor activation to initiate bottom-up propagation of the sensory information. **(B)** Mechanical forces at the whisker base upon whisker contacts as the animal approached the target (Axial force genotype effect: F = 88; p <0.001, 2-way ANOVA with df =1, Transverse force genotype effect: F = 113; p <0.001, 2-way ANOVA with df =1). **(C)** Change in Moment (M_z) at the follicle upon whisker contact (Genotype effect: F = 56; p <0.001, 2-way ANOVA with df =1). The data presented as mean ∓ std, blue denotes non-adaptive whisking conditions (SERT-/-, fluoxetine) and red adaptive whisking conditions (wild type, vehicle).

Given the observations outlined in Chapter 3 and 4, a computational circuit that could perform adaptive sensorimotor control necessarily requires information from sensory circuits about the stimulus availability as well as motor control circuits that perform phase to motor signal transformation given the current state of the sensory information. Based on the known coding properties of the neurons along sensorimotor circuits, and the connectivity between them (see Discussion), the graph network consists of the following nodes (Fig.4A): 1) primary somatosensory cortex (S1; barrel cortex) where stimulus properties are encoded (*42–48*); 2) primary motor cortex (M1) which provides adaptive motor control for whisker protraction (*49–53*), through recursively adjusting the amplitude and midpoint of whisking envelope (*54*); 3) central pattern generators (CPGs) that control phasic motion of whiskers (*55–57*); 4) superior colliculus (SC) which translates phase and amplitude information to motor control commands for facial motor nucleus (FMN) to drive whisking (*58*); 5) dorsal raphe nucleus (DRN) that regulates excitability in cortical and subcortical (sensorimotor) nuclei (*59*); and 6) a control circuit, plausibly the barrel cortex (*60*), that triggers whisker retraction upon stimulation to maintain touch duration (Chapter 3). In this model output of each node is a transfer function rather than a time and/or rate varying action potentials. Please note that the aim of this model is not to mechanistically explain how the brain performs sensorimotor computation, it is rather to provide the minimal circuit requirements for adaptive control of whisker position (see Discussion).

Simulations in this circuit showed that adaptive whisker protraction (Fig.4B, left) is an emergent computation and can be dysregulated by either removal of the serotonergic release or increasing the excitability in the sensory cortex, which was previously shown in SERT-/- animals (*27*) (Fig.4B, right). Although simulated animals, similar to rats (Fig.2), continue remapping whisker position as they approach the tactile target (Fig.4C), in circuits simulations without adaptive sensorimotor control do not result in change in increased whisker protraction, similar to the observations in SERT-/- and fluoxetine animals (Fig.4D, compare it to Fig.2B).

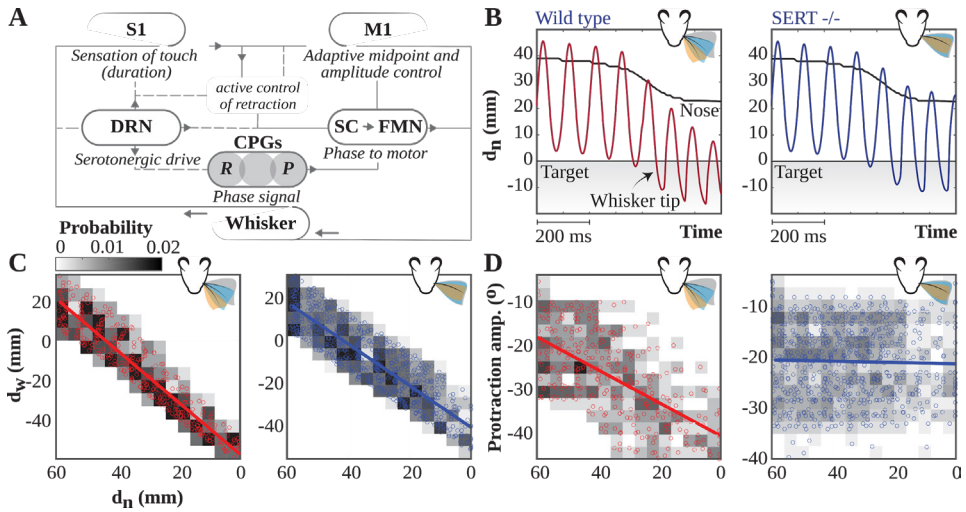

FIGURE 4. A computational circuit model of adaptive sensorimotor control. (A) Circuit components in the network: Barrel cortex subregion of the primary somatosensory cortex (S1), vibrissal motor cortex (M1), dorsal raphe nuclei (DRN), Superior colliculus (SC), central pattern generator (CPG) and facial motor nuclei (FMN) are modeled. See Discussion for details on the known anatomical and functional projections along this computational network. **(B)** Relative distance of a whisker tip to the tactile target during simulated adaptive whisking (red; left figurines) and simulated non-adaptive whisking (blue; right). The black line is an experimentally observed, randomly selected approach trajectory in a 2D plane, i.e. change in relative Euclidean distance to the target (d_n) as a freely behaving animal approaches a stationary tactile object. In adaptive whisking, sensory information modulates the motor command: protraction angle increases given the sensory information collected prior to the current whisk cycle, whisking amplitude decreases, and whisker retraction is actively controlled to keep the touch duration constant. **(C)** Simulated tip distance to target (d_w) in relation to body-to-target position. Left: adaptive whisking (red, r^2=%89); right: non-adaptive whisking (blue, r^2=%78). **(D)** Protraction amplitude, in respect to mid point, versus the nose distance d_n from target *in silico*. Left: adaptive whisking (red, r^2=%40); right: non-adaptive whisking (blue, r^2<%1).

Adaptive whisking improves tactile scanning resolution and this difference in whisking pattern is sufficient to explain the reduced sensory exploration during serotonergic dysfunction (seen in Fig. 1). The aforementioned computational model might help to unravel whether the reduced likelihood of tactile exploration observed in the SERT-/- and Fluoxetine groups is a product of the lack of adaptive motor control. To address this question I simulated sensorimotor exploration of a stationary target *in silico* (Fig.5). In this experiment the object was "touch transparent", as such contact with target did not change whiskers' motion trajectory. This is akin to the "virtual whisker tip position" mapping described previously (*1*) and ensures that intended whisker tip position could be visualized (Fig.5A).

The simulations showed that tactile navigation using adaptive whisker protraction results in *in silico* whiskers being positioned at the virtual target (Fig.5A, left) while non-adaptive whisking introduce localization errors (Fig.5A, right). These results could potentially explain the reduced tactile exploration observed in animals experiments (Fig.1E) with SERT-/- and fluoxetine injected animals. Indeed the likelihood of whisker contacts with the target observed *in silico* closely resemble the experimental observations (compare Fig.1E to Fig.5B). After the first touch event, the whisker motor commands are modulated and directed towards the target in adaptive whisking. This target alignment directly increases the probability of touch events.

Considering that the body locomotion together with whisking pattern govern the forces at the follicle, the localization errors observed during non-adaptive whisking could contribute to the reduction in mechanical forces transmitted to the follicle upon whisker contacts. Simulations showed that the contact induced forces were indeed significantly smaller during non-adaptive whisker protraction (Fig.5C). Larger touch induced mechanical information (i.e. force) at the follicle, improved tactile resolution (reduced localization error), and increased likelihood of sensory exploration argue that adaptive whisking results in higher signal to noise ratio during sensory acquisition.

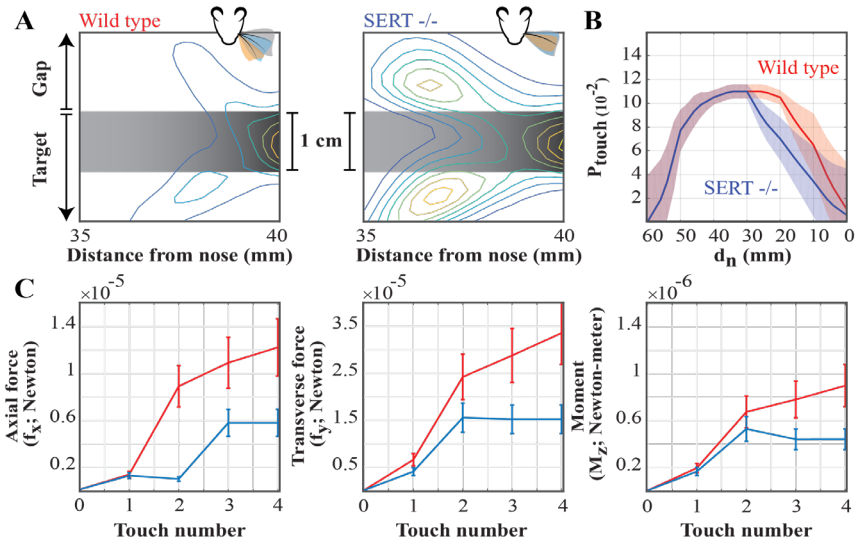

FIGURE 5. Lack of adaptive motor control alone is sufficient to explain the sensory exploration pattern after alterations in serotonin transmission. **(A)** Whisker tip position during exploration of a stationary target *in silico*. Grey shaded area represents the edge of tactile target. Density plots quantify the relative position of the whisker tip during tactile exploration with (Wild type: Contours are drawn with a step size of 16.5%, range: 16.5-100%) and in the

absence of (SERT-/- contours: step size of 12%, range: 9-100%) adaptive control of whisker protraction. **(B)** Probability of whisker contact with target *in silico*. Red: Adaptive whisker protraction (as seen in rats in wild type and vehicle injected groups); Blue: Non-adaptive whisker protraction (as performed by SERT-/- and after transient pharmacological intervention. **(C)** Mechanical forces (F_x and F_y) and Momentum (M_z) evolution at the whisker base (mean ∓ std) during simulated whisker contacts with tactile target *in silico*. Color code as in B. The approach trajectory for the adaptive and non-adaptive whisker protraction are based on behavioral observations. Touch number 0 in the X axis refers to the last whisking cycle prior to first contact with the target.

DISCUSSION

The present study demonstrated that genetically targeted or transient 5-HTT inactivation induce long-term impairment of sensorimotor computation, and interfere with the development of adaptive sensorimotor control during tactile object localization (Fig.2). Specifically, after serotonergic interventions animals failed to integrate sensory information to regulate the whisker positions in the subsequent whisk cycles. Nonetheless these rats were able to perform the object localization task successfully, similar to the wild-type and vehicle groups (Fig.1). In addition, results indicated that all animals across groups (wild-type, 5-HTT knockout, vehicle and Fluoxetine) had developed comparable goal-oriented locomotive strategies (Fig.1). To address whether changes in sensorimotor strategies alter sensory information mechanically transmitted along the whisker upon whisker contact, I analyzed the forces created at the follicle during active whisking. The results showed adaptive whisking maximizes the forces transmitted along the whisker (Fig.3). A computational circuit model of adaptive versus uniform (non-adaptive) whisking showed that inactivation of the communication between primary somatosensory and primary motor cortices impairs adaptive whisking sensorimotor control (Fig.4). The results also indicated that adaptive whisking improves tactile scanning resolution and confirmed the finding that adaptive whisking strategy increases sensory information transmitted during contact (Fig.5). Higher scanning resolution and stronger signal representation at the follicle translates to higher signal to noise ratio in sensory acquisition. The outcome of the simulation further proposed that the difference in whisking pattern between the two groups is sufficient to explain the sensory exploration pattern (seen in Fig.2) after alterations in serotonin transmission.

Serotonin plays an important role in development (see introduction and Chapter 1). Changes in the serotonergic drive might have long term behavioral consequences such as depression and anxiety (*14*, *19*, *61*, *62*), deficit in circadian rhythmicity (*19*), reduction in body weight (*14*, *61*), increased anti-social behavior (*19*), reduced sexual motivation (*19*, *63*, *64*), increased aggressive (*14*, *19*), and might impair reward processing and learning & memory (*19*). Impaired sensorimotor integration, upon serotonergic dysregulation, might contribute to expression of these phenotypes (*14*, *62*). Therefore serotonergic contribution to sensorimotor and cognitive processes might be causally related.

Altered serotonergic drive might result in miswiring of sensorimotor circuits, and thus cause sensorimotor deficits. Studies have shown that exposure to elevated serotonin level during the critical period disrupts locomotion (*14*, *19*, *21*, *23*, *65*), decreases novel object exploration (*14*, *19*, *26*) and causes delay in development of several reflexes and muscle strength (*14*, *18*, *21*, *22*) possibly via structural changes in the circuit organization (*19*). Alternatively, the sensorimotor deficits might be a by-product of altered balance between the excitation and inhibition. In our previous study (*27*), we demonstrated that high serotonin levels during development impair feedforward inhibition and facilitate excitatory drive in the somatosensory cortex. Disruption in the inhibitory drive can lead to malfunction of the network as these sensory evoked inhibitions participates in many aspect of sensory computation including: controlling precise timing of the response, preventing runaway excitation, sharpening stimulus selectivity, and increasing the overall sparseness of sensory response (*48*).

Network model of whisking

To provide a simplified circuit model of adaptive computation where serotonergic dysregulation to sensorimotor integration can be quantitatively studied, I have introduced a graph based network model whisking. The model is based on the known principles of neural representations and circuit connectivity across sensorimotor nuclei (see results and below). We have repeated the experiments in this chapter *in silico* to validate our model, and finally used it to address the circuit mechanisms of adaptive whisking.

Behavioral and in silico experiments showed that control animals (wild-type and vehicle groups) modulate the whisker protraction based on the recent sensory information by adjusting the midpoint of the whisking. While peak to peak amplitude of whisking decreases and whisking rhythm is regulated to keep the contact duration constant independent from the relative position of the body and whiskers in respect to the target. M1 is a possible candidate that controls the amplitude and midpoint of the envelope of whisking (*49*, *50*, *53*). Hill et.al (*54*), found that majority of single units in vM1 cortex code for variation in amplitude and midpoint of whisking. Since these motor representations were not influenced by inactivation of the trigeminal sensory input,

these signals are generated by a central source in M1. In our whisking network model, we have modulatory unit that applies the same controls on whisking pattern upon activation (see Figure 4A). When simulated whiskers contact the target, incoming sensory information drives the M1 module to apply goal-oriented modulation on whisking pattern. The peak to peak amplitude decreases and the maximum protraction angle increases.

Touch event influences the whisking pattern by driving the adaptive motor control as well as through a regulatory circuit that keeps the duration (duty cycle) constant (see Chapter 3). S1 (barrel cortical) neurons encode the touch event and its duration both at the single-cell and population levels (*42*, *46*, *47*, *66–69*). S1 spiking correlates with rapidly varying signal that represent the phase of the motion during rhythmic whisking (*42–45*). In addition S1 is linked to adaptive whisking, as this mode of whisking increases phase-locking between vibrissa movement and electrical activity in barrel cortex (*42*, *46*, *47*, *66–69*) while targeted stimulation of S1 results in whisker retraction (*60*). In our in silico model, S1 module senses the timings and whisker phase during a touch event. Information from S1 is ultimately integrated with the reafference copy (*70*) of the control signal in M1 to calculate the error between the planned whisking path and the current location (i.e. interrupted path) upon a contact event. Touch duration in S1 is further used to retract the whisker which ensures the constancy of touch duration. This calculation could originate in variety of brain regions (*60*). Mohan et.al (*71*), propose that the posterior parietal cortex might be the integrative hub.

In free whisking, rhythmic motion is the dominant mode of whisking (*72*). However, in adaptive whisking this rhythmic movement is altered by adjusting the whisk amplitude and midpoint of whisk cycle (*73*, *74*). M1 could have instructive role over this cyclical pattern of whisking (*75*). In our model we have two central pattern generator (CPG) modules, one for protraction, the other retraction generation. In the absence of sensory input (free whisking), the output of these two modules directly govern the whisking pattern. In case of contact, the M1 modules manipulates their output to instruct adaptive whisking, possibly via superior colliculus (*58*).

Serotonergic system contributes to sensorimotor system prominently through its projections via DRN (see Chapter 1 for review). Altered serotonin level, could disturb the sensorimotor network configurations and its within communication. In the current model, DRN governs the communication among our modules. Here, the effects of disrupted communication among whisking related nuclei on sensorimotor computation is simulated.

The final motor command (whisker angle/phase) is connected to a virtual model of whisker (*31*, *34*). Our whisker is modeled with a parabola and bends upon contact. We use the egocentric information of the whisker position combined with allocentric information of body-to-target position of the animal in the simulation as input to our whisker model. Using this model we calculate the bending along the whisker and the forces at the whisker's base. The body locomotion (allocentric) information in simulation is learned and determined through experimental data of rats performing gap crossing task. Using this in-silico whisker model, the consequences of adaptive motor control on sensory acquisition is simulated.

OUTLOOK

The present study demonstrates that reduction of 5-HTT during early development, either by blocking 5-HTT using an SSRI (fluoxetin) or constitutively by genetic deletion of 5-HTT, have long-term effects on sensorimotor computation and impairs emergence of adaptive whisking. As a result whisker contacts transmit less mechanical information to whisker follicle. Considering our previous observations on the reduction of inhibitory drive and increased feedforward excitation in the primary somatosensory cortex (*27*), and the observations that SERT-/- deletion reduces the thalamocortical projections targeting the cortical layer 4 (*76*), it is tempting to speculate that the change in cortical excitability is an compensatory change to facilitate the detection of weak signals originating from the periphery. Regulating the excitability of the inhibitory neurons in Layer 4 in a cell type specific manner during object localization will provide a mechanistic insight on the neural basis of touch sensation. Re-balancing the excitatory and inhibitory drive in the somatosensory cortex will also alter the communication between S1 and M1, thus might rescue the motor phenotype described herein.

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5

Adaptive sensorimotor control as a filtering process

Humans exhibit mastery in solving complicated sensorimotor control behaviors from picking up an egg to hitting a tennis ball. This adaptive computation solves complexities inherent in motor control such as conduction delays and (neural) noise in sensory and motor circuits, while accounting for the nonlinearity, nonstationarity and uncertainty of the control plant and environment (*1*–*3*).

The optimal solution for adaptive motor control requires coupling of motor control to sensory feedback (*3*, *4*). These sensorimotor transformations are the first complex computations that neural circuits learn. As baby brains perform thousands of trial and error to generate stimulus (and eventually context) specific actions, distributed networks in the brain implement a set of forward models[2] (*3*, *5*, *6*) to excel in sensorimotor transformations. Although these computations are at the basis of all goal-directed behavior throughout life, and decoupling of sensory feedback from motor control results in failure of sensorimotor transformations (*7*, *8*), their unifying computational principles are yet to be discovered.

In this thesis, I addressed the development and computational principles of adaptive sensorimotor control in the whisker system. Mice and rats commonly utilize their whiskers to navigate, locate and/or discriminate objects in darkness (*9*–*13*). In **Chapter 1**, I reviewed the whisker sensorimotor system, including its ascending and descending pathways together with the postnatal development of the barrel system, and the role of serotonin in its development and function. This Chapter also gave rise to a critical review (*14*) that addresses the principles of information processing along sensorimotor systems (see Publications for the details of all manuscripts originating from this doctoral research).

To study principles of sensorimotor computation one needs to precisely quantify behavior. Therefore I deployed a custom robotic apparatus to train animals on an object localization task. The robotic trainer has integrated high-speed imaging and motion sensing capabilities that enables observation of sensorimotor behavior with high spatial (i.e tens of micrometers) and temporal (~2.5 ms) resolution. Using this robot, hundreds of rats and mice across various experimental conditions and developmental ages were trained. A total of 6642 trials of experimental data, i.e. freely moving animals spontaneously exploring their environment and successfully locating a stationary object in darkness using their whiskers, were collected. The behavioral data from these experiments are described in **Chapter 2** and made publically available. Chapters 3-4 make use some of the data provided in this database.

2 Forward model is a control process to predict the next state of an actor, e.g. a robotic agent, body, appendage or whisker position. It requires knowledge about the current state of the actor and the motor command.

In **Chapter 3**, I longitudinally studied the development of sensorimotor computation in juvenile rats (~P21) and after they reach adulthood (~P65) as they performed tactile object localization. The results showed that adaptive sensorimotor control does not mature during the first three weeks of the postnatal development, a period known to be critical

for functional neural circuit formation along the sensorimotor axis. Juvenile rats successfully located tactile targets, adapting their body position to locate stationary targets in darkness. Unlike adult animals, however, juvenile rats failed to adapt their whisker protraction to sensory information they collected in preceding whisk cycles. As a result juvenile rats continue to whisk at a constant amplitude independent from their distance to the tactile target (see Figure 1).

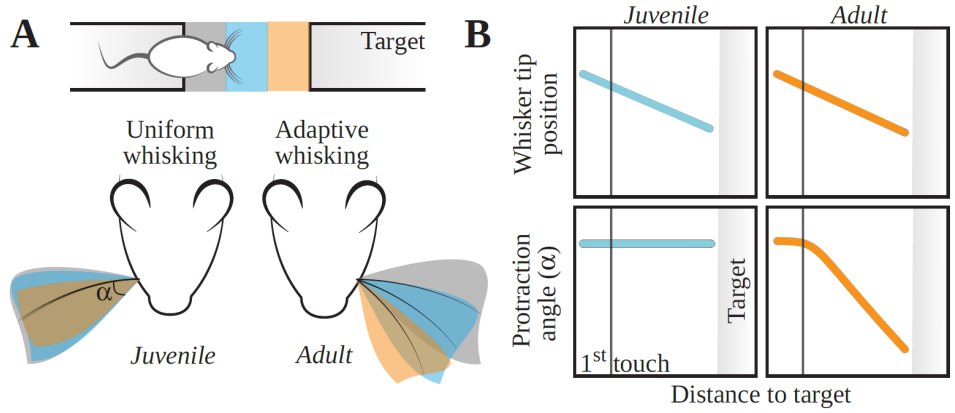

FIGURE 1. Adaptive sensorimotor control of whisker protraction develops later in life. (A) Whisker protraction amplitude and whisker position at rest (i.e. mid-point between the protraction and retraction set-points) during stationary object localization. Animals younger than 1 month old whisk with constant protraction amplitude independent from their distance to the tactile target. Adult animals utilize adaptive whisking, modulate where they position their whiskers and how much they protract them, based on recently acquired sensory information. **(B)** Whisker tip position (which is a result of the change in body position and active whisking) and whisker protraction amplitude across the developmental ages. Note that juvenile animals do not adapt their whisker protraction based on the change in the body position, although they adaptively adjust their body to target distance at this age. See Chapter 3 for details.

Chapter 3 is concluded with a computational model of adaptive control of whisker position. Based on the experimental observations, the model heuristically links the different stages of sensorimotor computation for object localization. It numerically models the actual (sensed) haptic feedback as rodents form a percept of target location,

while novel sensory information recursively modulate motor control. Simultaneously, haptic feedback interrupts motor plans through reactive retraction of whisker to maintain touch duration.

Considering that sensorimotor computation for adaptive whisker positional control matures postnatally, I reasoned that alterations in neural circuit formation during early postnatal development could shape maturation of active sensing. Sensorimotor integration is modulated both during development and in the adulthood by top-down processes, including animal's state, context, expectations, and task requirement which are, neuronally, maintained by neuromodulatory neurotransmitters (*15*, *16*). Among the neuromodulatory transmitters, serotonin contributes to motor control both at the level of rhythmic motor control via modulation of CPG action, as well as in the context of motor learning (*17*). In addition, serotonin potently alters network formation thus changing serotonin levels during development could potentially impair the maturation of sensorimotor computation (*17*). Therefore, in **Chapter 4,** I quantified adaptive whisking behavior upon transient and during sustained impairment of serotonergic signaling. The results showed that postnatal development of adaptive motor control requires intact serotonergic signaling and even transient modulation of serotonergic signalling, early during development, impairs sensorimotor computations in adulthood. *In silico* experiments performed on a computational model of whisker sensorimotor system introduced in the Chapter showed that these observations can be explained by a simplified network model of sensorimotor control, and detailed the sensory consequences of adaptive motor control.

SENSORIMOTOR CONTROL AS A FILTERING PROCESS

The optimal control solution for tactile navigation necessarily requires coupling of motor control to sensory information and feedback, as the sensory world is often unpredictable and rarely constant (*3*, *4*, *18*). This integration enables recursive update of various internal models (let it be the target location, stimulus percept or action plan) using any knowledge available to the brain, e.g. incoming sensory information, internally generated (top-down) information, and contextual knowledge (*3*). This type of computation is frequently defined as a filtering problem.

During stationary tactile object localization on the gap-crossing task (*12*, *19*, *20*), for example, rats and mice sample (palpate onto) the tactile target multiple times before forming a decision about where the target is, and where to navigate next in

this environment (*12*, *19–23*). With each whisker contact, they presumably compose a percept of the object, including its location, and integrate these precepts across iterations to form a decision and update it as necessary. Therefore, the motor control plant that performs whisker positional control should be calculating a state estimate of target location in the n^{th} iteration, using prior (n-1) location estimate, efference copy of whisker motor command, and sensory information available at the periphery.

A filtering framework that grants such an integration could be represented by Bayesian inference (*2*, *24*, *25*). Bayesian inference provides the utilities to combine the statistical distribution of possible states of the world *a priori* (also termed as an internal model of the external world), with sensory information and motor commands (*24*, *25*). Although its neuronal mechanisms are *currently* unknown, the brain might implement this inference by updating its prior knowledge (learned transformations), given the current/recent or predicted sensory information along with the efference copy of internally generated motor commands (motor intentions) (*4*). In terms of adaptive motor control, the posterior in this process is the brain's best guess for the current state of the body and world, as well as how to act on the world given the current state of the body. In this chapter, I propose that adaptive motor control and its sensory consequences are "filtering" processes that ultimately enable sensation-perception-action and two-way communication between the body and world. By postulating the sensorimotor computation as a Kalman filter (*24*), an expansion of Bayesian inference for multivariate (normal) distributions (*26*), the results obtained in this thesis could be implemented recursively, modifying motor commands used for predictive control, and consecutively altering the processing of both the (near) future sensory information and brain's certainty about the state of world.

INTERNAL MODELS OF THE BRAIN AS BASIS FUNCTIONS FOR THE FILTERING PROCESS

During sensorimotor computation, motor behavior adapts to the context and task requirements as sensory information is used to plan and update the motor command to enable adaptive sensing. Extraction of task related information (*27*) has been studied extensively, e.g. during saccadic eye movement and inattentional blindness (*28*) in humans, and during whisker based active sensing in rodents (*19*). This motor adaptation might be implemented by forming internal models of the action, which could be constructed through measuring the difference between predicted (intended, internally generated) and actual (sensed) motor action (*3*, *18*, *29–31*). Adaptive sensorimotor

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computation enables the system to decode the causality between its motor actions and corresponding sensory feedback, results in sensory consequences of motor actions to be predicted with higher accuracy and lower computational cost (*19*, *32*) and ultimately enables the body to act and react on the world.

Adaptive sensorimotor control assumes co-maturation of sensory and motor systems to optimize task performance and predictive models of action generation (*3*, *33*). However results in Chapter 3 argue that afferent (sensory) pathways mature prior to emergence of adaptive sensorimotor control (at least in the whisker system). Given that i) rodents can detect whisker touch and learn to relate passive whisker contacts to task outcomes prior to whisking onset (*34*), ii) transient disturbance of network formation during early postnatal development results in long-lasting impairment of adaptive sensorimotor control (Chapter 4), adaptive motor control emerges only after functional maturation of the afferents.

During the formation of internal models of the body and world, relying on sensory feedback alone exposes the system to delay, noise and uncertainty (*2*, *3*, *18*, *35*, *36*). To overcome these limitations brain uses higher order (internal) models of consequences of its actions for inference and prediction (*2–4*, *37*). Sensorimotor learning in its essence involves optimization of these models (*25*, *37*). Predictive control through forward models can improve the system's sensitivity to delays in sensory feedback, reduce its vulnerability to noise, accounts for the sensory consequences of self-generated motion, and can facilitate learning of sensorimotor transformations by generating an error signal (*25*, *37*). To perform these computations, predictive control uses an efference copy of the motor command and ultimately estimates the sensory and motors states, predict the sensory feedback (*1*, *3*, *4*). In principle, in *predictive control,* detecting the difference between predicted and actual sensory information (i.e. error signal) enhances task related knowledge and improves the precision of future action (*16*). If the brain were to rely solely on the predictive control, however, the internal models would be updated (relatively) slowly as the only sensory information relevant for motor control would be the information collected in the past (*19*). Instead the brain also utilizes the current sensory information to update its internal models in real-time using *reactive control*. This control scheme relies on fast reactive feedback loops which bypass previously generated command and is based on the stimulus valence of the current sensory information (chapter 3, (*38–40*)).

In a control system that utilizes two schemes (predictive vs reactive), Bayesian inference could play an integrative role to define how new information might be optimally

combined with prior beliefs. Since prediction based on forward models suffer from noise, uncertainty, and non-stationary nature of the system (*2*, *3*, *18*, *35*, *36*), in the absence of sensory feedback the predicted state will drift from the actual state over time. In our sensorimotor task for instance, Bayesian inference provides a numerical estimate of the probability of receiving certain sensory feedback (location of an object) given animal's current position, knowledge (allocentric and egocentric), expectation (state) and a copy of the last motor command generated. This estimation also requires an internal model of the control plant, which could be inferred from whisking kinematics, to predict the prior-posterior transformations. Assuming that relevant variables are sampled from a normal distribution the Bayesian filter could be represented by Kalman filter (*24*, *26*).

Kalman filter is a recursive filter that estimates the internal state of a system through a two-step process of *prediction* and *update* (see Information box; to the right). For *prediction*, Kalman filter determines the estimates of current state variables, and their uncertainties (accuracy of the state estimate). When novel (sensory) information arises those predictions are updated (integrated with sensory state estimates) using a weighted average, with higher gain assigned to estimates with higher certainty. Kalman filter is similar to hidden Markov layer (*41*), since its current state solely depends on the previous state, current measurements and an uncertainty matrix. Kalman filter naturally lends its computations for sensorimotor control since it employs a system transition model to update its state estimates when new (sensory) information arises. This way the system considers the delay between motor command and the subsequence sensory feedback. Combining the prediction with measurements results in more accurate estimations than those based on a single measurement alone, through estimation of a joint probability distribution.

Kalman filter and its extensions perform not only **filtering** (i.e. estimating the current value given past and current observations), but also **smoothing** (i.e. estimating past values given present and past observations to update internal models) and **prediction** (i.e. estimating the future information given the present and past observations). Therefore it could be used to formalize and numerically study sensorimotor computation, behaviorally, neuronally and statistically. Accordingly, the Kalman filter is commonly used to model Bayesian decision making in cognitive neuroscience (*24*, *42*, *43*). It has been used to model, predict and replicate human behavior while behavior evolves over time (*43–46*). In addition, Kalman filters have been used to optimally predict sensory consequences of motor control, integrate sensory and body posture signals, and estimate motor control commands (*43*). Neuronally, they have been deployed to simulate dynamics of a single neuron, to address the modulatory dynamics of oscil-

latory waves in brain, to develop a control framework for Parkinsonian dynamics (see (*47*) for a review), and to decode neural activity to infer movement kinematics (*48–50*).

Kalman filter

Kalman filter is an iterative process of "Prediction" and "Update". In the prediction step Kalman filter produces an *a priori* system state estimate from the previous state, using state transition model. During update, it uses the sensory information to produce an *a posteriori* state estimate, based on the priori estimate. Two steps of Kalman filter is shown below: $\boldsymbol{F}$ is the state transition model matrix. $\boldsymbol{B}$ is the control input model applied to the control vector $\boldsymbol{u}$. $\boldsymbol{H}$ is the observation model matrix, it maps the state vector space into the observed vector space. $\boldsymbol{z}$ is the observation vector obtained from sensors. $\boldsymbol{K}$ is the optimal Kalman gain matrix, it determines the importance of the innovation. $\boldsymbol{P}$ is the error covariance matrix, it is a measure of the estimated accuracy of the state estimate. $\boldsymbol{Q}$ is the process noise covariance matrix. $\boldsymbol{R}$ is the observation noise covariance matrix.

Prediction step

Predicted state $\hat{\mathrm{x}}_{\mathrm{k|k-1}} = F_k\,\hat{\mathrm{x}}_{\mathrm{k-1|k-1}} + B_K u_k$

Predicted error covariance $\hat{\mathrm{P}}_{\mathrm{k|k-1}} = F_k\,\hat{\mathrm{P}}_{\mathrm{k-1|k-1}} F_k^T + Q_k$

Update step

Innovation $\hat{\mathrm{y}}_{\mathrm{k}} = z_k - H_k\,\hat{\mathrm{x}}_{\mathrm{k|k-1}}$

Optimal Kalman gain $\mathrm{K}_k = \mathrm{P}_{k|k-1} H_k^T / (R_k + H_k \mathrm{P}_{\mathrm{k|k-1}} H_k^T)$

Updated state estimate $\hat{\mathrm{x}}_{\mathrm{k|k}} = \hat{\mathrm{x}}_{\mathrm{k|k-1}} + K_k \widehat{y_k}$

Updated estimate covariance $\hat{\mathrm{P}}_{\mathrm{k|k}} = (I - K_k \mathrm{H}_k)\hat{\mathrm{P}}_{\mathrm{k|k-1}}(I - K_k \mathrm{H}_k)^T + K_k R_k K_k^T$

ADAPTIVE WHISKING REDUCES NOISE AND INCREASES CERTAINTY ABOUT STIMULUS: A LINEAR UNIVARIATE IMPLEMENTATION OF THE KALMAN FILTER

In sensory driven adaptive motor control paradigms, motor commands are continuously updated to maximize task performance. In the whisker system, this adaptation is implemented recursively based on sequential emergence of sensory information (chapters 3 & 4, *19*). During adaptive whisking, rats/mice actively control the mid-point and amplitude of whisking which results in incremental increase of protraction angle and decrease in the amplitude of whisking (Chapter 3). It has been shown that this behavior maximizes the spatial resolution in whisker touch and minimizes the localization errors (or lowers process noise) during whisker protraction (Chapter 4). In addition, adaptive whisking increases the mechanical information transmitted along the

whisker (Chapter 4) which results in higher signal to noise ratio and lower covariance of the sensory acquisition noise.

Kalman filter framework demonstrates how these results manifest, and that adaptive whisking reduces uncertainty during whisker based object localization. My objective here is not to propose that central nervous system adopts strategies identical to Kalman filter, I rather suggest that both are strongly similar in their Bayesian nature of integrating forward model predictions with sensory information. Unscented Kalman filtering or Particle Filtering might simulate cognitive processes more accurately due to their ability to handle nonlinear and multivariate systems, however, their Bayesian framework is similar to Kalman filtering (*47*).

For adaptive control of whisker position during tactile navigation the current state (forward model, ***F*** in Kalman equations, see the information box in the preceding section), previous state estimate (a memory term), and efference of motor command (***B*u***) need to approximated. Recursive update of motor commands results in lower process (***Q***) and sensory noise (***R***) which increase the Precision of prediction and sensory update, respectively (Chapters 3 and 4). The state estimate can be realized as the joint probability distribution of prediction and update; its error covariance (***P***) is thus related to ***Q***, ***R*** and ***F***. In each iteration, past state estimation (based on n-1 observation) is used to predict the current state and the outcome is combined with novel sensory information to increase the certainty of object location. This process is akin to decreasing the standard deviation of the state estimate distribution and increasing the animal's certainty about target location. Lower covariance between the sensory acquisition noise and the process noise reduces the error covariance and innovation (the residual between predicted state and measured state) in Kalman filter (see Figure 2 simplified flow-chart). In the framework of feedforward control, this is functionally equivalent to reduced uncertainty about the target location and increased redundancy of the future sensory information (given the reduced innovation).

The proposed Kalman filter, predicts n^{th} state estimate using solely the previous (n-1) state estimate and efference copy of motor control, significantly simplifying the design of the controller. This prediction will be updated with sensory information using optimal Kalman gain to form a posteriori state estimate of object´s location. In every iteration, integration (joint probability distribution) of priori state estimation and novel sensory information forms a more accurate percept of the location with reduced standard deviation of the error distribution (σ_E) around the perceived location. This iterative procedure continues until the standard deviation of decision error is reduced below a (dynamic) threshold.

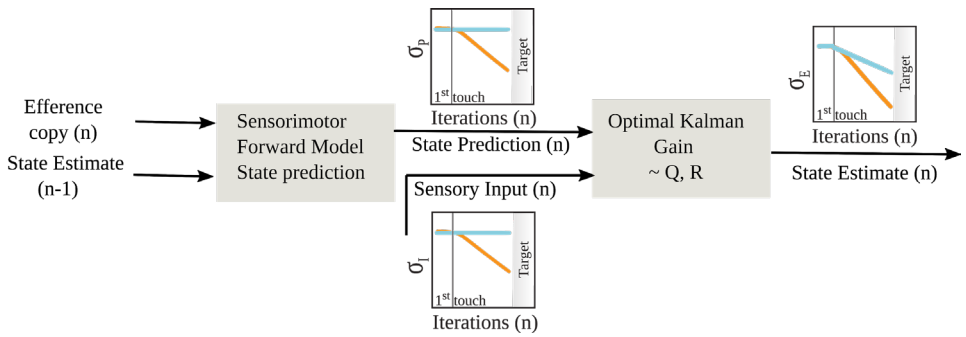

FIGURE 2. Adaptive control of whisker position from a Kalman filter perspective. See main text for details.

During adaptive whisking, motor controls are being recursively modified by sensory inputs, which reduces the standard deviation of prediction (σ_p) and sensory input (σ_I) error probability distributions. Reduction in the error covariance grants the system higher certainty in comparison to a non-adaptive system where error covariances stay constant across iterations. Thus, in the absence of adaptive sensorimotor control, system requires more iterations of sensory acquisition to achieve similar decision certainty, explaining the empirical observations in Chapter 3.

In solving sensorimotor control problem, the system should be able to deal with nonstationarity and noise. In the proposed model the filter adapts to such changes by iteratively adjusting its error covariance and reaches an optimal solution through balancing the gain between prediction (performed by the feedforward model) and update (via sensory information). Alternatively the computation can integrate information across domains (e.g. body position vs whisker position vs absolute and relative target location). This is particularly relevant during tactile navigation in freely behaving animals as the animal needs to encode the target location both in egocentric and allocentric coordinates while discounting the changes in body position from the amplitude of whisker protraction to ensure constancy of the tactile space. Change in one domain requires optimization in others to achieve optimal solution. This could be achieved by transfer functions that enable transformations across domains (see implementation example in Figure 3). These transfer functions could be a possible framework to pass the knowledge through the network and reduce cost of optimization in all network levels.

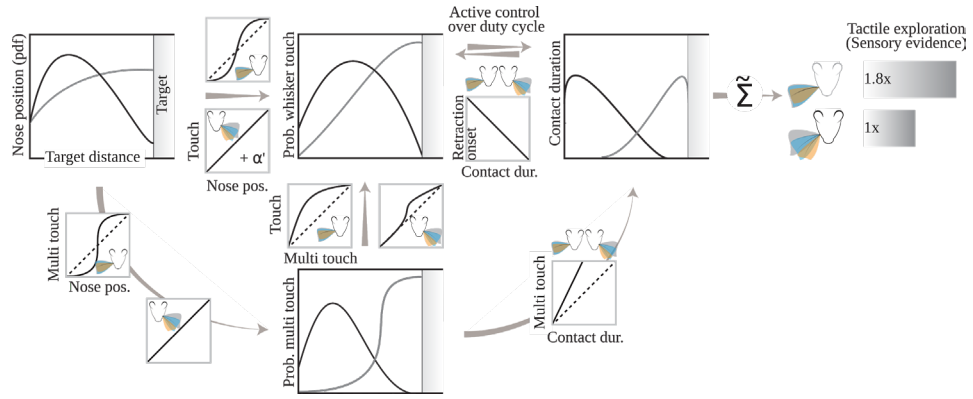

FIGURE 3. Learned transfer functions in adaptive versus non-adaptive sensorimotor control. Inferred transfer functions are based on the behavioral data. Young adult and juvenile rats employing adaptive versus non-adaptive sensorimotor control are demonstrated. These transformations might explain how locomotion strategies together with adaptive whisking explain the difference in sensory acquisition.

OUTLOOK

This thesis provided an in-depth and quantitative insight on how rodents locate stationary objects using their whiskers. The control theory outlined in the current chapter opens new avenues in research where distributed neural recordings across neural loci of interest together with targeted modulation of neural activity will help to determine the neural basis of sensorimotor computation by taking advantage of the predictive nature of these control models.

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Summary

SUMMARY

How does brain perform sensorimotor computations is a cardinal question in system neurosciences. To calculate this complex task, brain uses its prior knowledge, e.g. current/recent or predicted sensory information as well as the efference copy of internally generated motor commands. Action execution based on this computation results in sensory exploration, creating a perpetual interaction between the sensory and motor streams in the brain.
During the sensorimotor computation, motor behavior adapts to context and task requirements as sensory information modulates the motor command to enable adaptive sensing, and presumably to optimize the behavioral performance. In an object localization task, for example, this adaptive modulation enables goal-directed motor control which increases signal to noise ratio in neural representations while reducing the processing load in sensory organs. This active sensorimotor process takes into account the entire body motion, as neural computations compensate for the change in body position including the sensory organ motion. Integrated sensory information in the context of internally generated action motor commands enable the brain to form a prediction of object location in relation to the body (in egocentric coordinates) as well as in respect to the sensory world (i.e. in allocentric coordinates).

The rodent haptic system provides an excellent model to study sensorimotor computation. In the absence of auditory and visual information, mice and rats, due to their nocturnal habits and subterranean habitats in the wild, commonly utilize touch to navigate, locate and/or discriminate objects. Among the touch receptors in the body, those embedded in the whisker follicles are particularly of interest to whisking rodents, as they sweep their whiskers in air periodically to examine their surroundings.

This thesis is an endeavor to decode how brain performs sensorimotor control as freely moving animals perform object localization by active whisking. The questions addressed include how does brain combine feedforward motor predictions with sensory feedback to execute goal oriented movements? How do these computations emerge during postnatal development as animals learn to integrate sensory information to generate motor action? What are the possible neuromodulatory mechanisms behind the development of sensorimotor computation? And, how does the adapted motor control alter sensory experience?

The whisker sensorimotor system, including its ascending and descending pathways is reviewed in **Chapter 1**. This chapter further elaborates on the postnatal development of the barrel system and the role of serotonin in its development and function.

Understanding the mechanisms of tactile sensorimotor computations during active sensing necessarily requires precise quantification of the sensory input and motor output behaviorally. In the whisker system this could be achieved by quantifying whisking characteristics (such as whisker position, frequency, amplitude, velocity) and capture the touch statistics (e.g. touch position, contact induced displacement of whiskers, touch duration). In **Chapter 2** using a robot to train rats and mice across various experimental conditions, I present a big dataset that includes over 6000 high-speed videos of animals locating stationary object in space. This data are used to describe the principles of sensorimotor computation during navigation as exemplified in Chapters 3-4.

Nature and nurture influence the development of cortical neural networks. Experience dependent and independent cues together govern formation of these networks throughout life. In particular the first three postnatal weeks are critical for the anatomical, functional and behavioral maturation of cortical circuits. In **Chapter 3**, I longitudinally studied the development of sensorimotor computation in juvenile rats (~P21) and after they reach adulthood (~P65) while they performed a tactile object localization task. The results indicate that although juvenile rats are capable of successful object localization, their sensorimotor strategy matures only later in life; (young) adult rats employ adaptive strategies for sensorimotor computations, which juvenile rats lack. Juvenile rats whisk uniformly throughout the entire object localization epoch, and do not adapt their locomotion strategies according to sensorimotor task requirements. On the other hand, adult rats actively control the mid-point and amplitude of whisking, and incorporate body locomotion to calculate whisker position in the next whisking cycle, resulting in adaptive positional control of whiskers during tactile navigation. A computational model of the adaptive motor control of whisker position is provided to heuristically link the different stages of sensorimotor computation during object localization.

Active sensing requires adaptive positional (motor) control of sensory organs based on the contextual, sensory and task requirements. As discussed in Chapter 3, in the whisker system, adaptive motor control for goal-directed action develops postnatally after the maturation of intracortical circuits. Perturbations with sensorimotor network connectivity could potentially alter the maturation of sensorimotor computation. Serotonin has been shown to be among cardinal influencers on network formation, during and after developmental period, thus changing serotonin level during develop-

ment could potentially alter the maturation of sensorimotor computation. In **Chapter 4**, I tested this hypothesis in serotonin transporter knock-out animals and after transient intervention with serotonin signaling during postnatal development. The results showed that sustained alterations of serotonergic signaling impairs emergence of sensorimotor adaptation in adulthood. A direct outcome of this altered motor control is that mechanical forces transmitted to the whisker follicle upon whisker contacts are reduced, suggesting that increased neocortical hyperexcitability after altered serotonergic signaling (Miceli et al, 2017) is not because of a peripheral change in sensory organ use. These results argue that postnatal development of adaptive motor control requires intact serotonergic signaling, and that even transient alterations in serotonergic signalling early during development causes long-term sensorimotor disturbances in the adulthood. Experiments using the computational model of whisker sensorimotor system showed that these observations can be explained by a holistic network model of sensorimotor computation, and detailed how this alteration in network controls forces created at the follicle and decreases the tactile resolution.

In **Chapter 5**, I provide an overall discussion of the research presented herein and postulate object localization as an adaptive motor control problem that could be explained by Bayesian filtering. Supported by the empirical observations in this thesis, I propose that the brain solves this problem using an iterative process that involves dynamic update of an internal model of the sensory world. I further argue that adaptive whisking increases certainty in object localization task by reducing the sensory and process noise. While performing this computation, brain encodes sensory information first in egocentric coordinates and subsequently utilizes learned transfer functions to translate sensory information into motor action. The behavioral outcome of this computation is the adaptive sensorimotor control for navigation.

Nederlandse samenvatting

SAMENVATTING

Adaptive sensorimotor control for navigation

Adaptieve sensomotorische controle voor navigatie

Één van de hoofdvragen binnen de systeem-neurowetenschap is hoe het brein sensomotorische berekeningen uitvoert. Om deze complexe taak te volbrengen, gebruikt het brein voorgaande kennis, zoals huidige, recente of voorspelde sensorische informatie, samen met intern gegenereerde efferente kopieën van motorische handelingen. Uiteindelijk zorgen deze computaties ervoor dat een dier z'n omgeving kan verkennen, waardoor de interactie tussen sensorische en motorische informatie in het brein in stand wordt gehouden.

Tijdens de sensomotorische berekeningen wordt de motoriek aangepast aan de context en de taak, waarbij sensorische informatie gebruikt wordt om de motoriek te moduleren. Op deze manier kan op een adaptieve manier worden waargenomen, en wordt waarschijnlijk het resultaat van het gedrag geoptimaliseerd. Tijdens een taak waarbij waarbij een object moet worden gelokaliseerd, bijvoorbeeld, zorgt deze 'adaptieve modulatie' voor een doelmatige motorcontrole, wat de signaal-ruisverhouding verhoogt en tegelijkertijd de werkdruk van de zintuigen verlaagt. Tijdens dit actieve sensomotorische proces wordt rekening gehouden met bewegingen in het gehele lichaam, zodat neuronale berekeningen compenseren voor veranderingen in zowel de positie van het lichaam als die van het zintuig. Geïntegreerde sensorische informatie, in de context van intern gegenereerde motorbevelen, zorgen ervoor dat het brein een voorspelling kan maken over de locatie van een object ten opzichte van het lichaam (d.w.z. in egocentrische coördinaten) en de sensorische wereld (in allocentrische coördinaten).

Het haptische systeem van knaagdieren is een uitstekend model om sensomotorische computatie te bestuderen. In de afwezigheid van auditieve en visuele informatie gebruiken ratten en muizen, omdat het nachtdieren zijn die vaak ondergronds verblijven, vaak aanraking (haptiek) om te navigeren en om objecten te lokaliseren en/of te onderscheiden. Van alle tastreceptoren in hun lichaam zijn die in de snorhaarfollikels van bijzonder belang voor knaagdieren die hun snorharen actief bewegen om hun omgeving te verkennen.

In dit proefschrift wordt gepoogd om te decoderen hoe het brein sensomotorische controle uitoefent als vrijelijk bewegende dieren een object lokaliseren door middel van hun snorharen. De vragen die aan bod komen zijn: "Hoe combineert het brein

motorische voorspellingen met sensorische feedback om doelgerichte bewegingen uit te voeren?", "Hoe komen deze computaties tot stand tijdens de postnatale ontwikkeling, wanneer dieren leren om sensorische informatie te integreren om motorische taken uit te voeren?", "Wat zijn de mogelijke neuromodulatie-mechanismen achter de ontwikkeling van sensomotorische computatie?" en "Hoe beïnvloedt adaptieve motorcontrole de zintuiglijke ervaring?".

Het sensomotorische systeem van de snorharen, inclusief de opwaartse en neerwaartse routes, wordt besproken in **Hoofdstuk 1**. Dit hoofdstuk wijdt ook uit over de postnatale ontwikkeling van het *barrel*-systeem en de rol van serotonine in de ontwikkeling en functie ervan.

Een begrip van de mechanismen achter sensomotorische computaties van de tastzin tijdens actieve waarneming vereist een precieze kwantificatie van de sensorische input en de motorische output in de vorm van gedrag. In het haptische systeem zou dit kunnen worden bereikt door kwantificatie van de karakteristieken van snorhaarbewegingen (zoals hun positie, frequentie, amplitude en snelheid) en tegelijkertijd de statistieken van de tast (bijvoorbeeld aanrakingspositie, buiging van de snorharen, duur van de aanraking) vast te leggen. In **Hoofdstuk 2** gebruik ik een robot om ratten en muizen te trainen in verschillende experimentele condities, en presenteer een grote dataset met daarin ruim 6000 hogesnelheidsvideo's van dieren die een stilstaand object in de ruimte trachten te lokaliseren. Deze data kunnen worden gebruikt om de principes van sensomotorische berekeningen tijdens navigatie te beschrijven, zoals wordt gedaan in Hoofdstukken 3 en 4.

Aanleg en opvoeding (*nature* en *nurture*) beïnvloeden de ontwikkeling van corticale neurale netwerken. Ervaringsafhankelijke en -onafhankelijke signalen bepalen samen de formatie van deze netwerken gedurende het leven van een organisme. Vooral de eerste drie postnatale weken zijn kritisch voor anatomische, functionele en gedragsgerelateerde maturatie van corticale circuits. In **Hoofdstuk 3** heb ik over een lange termijn de ontwikkeling gevolgd van de sensomotorische computaties in ratten op jonge leeftijd (~P21) en nadat ze volwassen waren (~P65) bij het uitvoeren van een object-lokalisatietaak. De resultaten geven aan dat hoewel jonge ratten objecten succesvol kunnen lokaliseren, ze hun sensomotorische strategie gedurende hun leven aanpassen. (Jong)volwassen ratten gebruiken adaptieve strategieën voor hun sensomotorische berekeningen, die bij jonge ratten nog ontbreken. Jonge ratten gebruiken hun snorharen op uniforme wijze gedurende de taak, en passen hun bewegingsstrategieën niet aan op basis van de vereisten van de taak. Volwassen ratten,

daarentegen, bepalen actief het middelpunt en de amplitude van de bewegingen van hun snorharen, en incorporeren bewegingen uit het gehele lichaam om de positie van snorharen in de volgende bewegingscyclus te berekenen, wat resulteert in een adaptieve controle over de positie van hun snorharen tijdens het gebruik van de tastzin. Ook wordt in dit hoofdstuk een computermodel van de adaptieve motorcontrole over snorhaarposities voorgesteld, waarmee de verschillende stadia van sensomotorische computaties tijdens object-lokalisatie kunnen worden verkend.

Actieve waarneming vereist een adaptieve positionele controle over de zintuigen die gebaseerd is op context en de vereisten voor de waarneming en het uitvoeren van een taak. Zoals besproken in Hoofdstuk 3, ontwikkelt adaptieve motorcontrole voor doelbewuste acties zich in het 'snorhaarsysteem' van knaagdieren na de maturatie van intracorticale circuits. Verstoringen binnen de connectiviteit van het sensomotorische netwerk zouden mogelijk ook de ontwikkeling van sensomotorische computaties kunnen veranderen. Serotonine staat bekend als één van de grootste invloeden op netwerkformatie tijdens en na de ontwikkelingsperiode. Het veranderen van de serotonine-niveaus tijdens de ontwikkeling zou daarom mogelijk de ontwikkeling van sensomotorische berekeningen kunnen beïnvloeden. In **Hoofdstuk 4** heb ik deze hypothese getest in serotoninetransporter-*knockout*-dieren en na een tijdelijke beïnvloeding van serotonine-communicatie tijdens de postnatale ontwikkeling. De resultaten laten zien dat langdurige verandering van serotoninesignalen de totstandkoming van sensomotorische adaptaties in het volwassen dier remt. Een direct resultaat van deze veranderde motorcontrole is dat er minder mechanische kracht wordt doorgegeven aan de snorhaarfollikel als snorharen objecten aanraken, wat aangeeft dat een verhoogde exciteerbaarheid in de cortex van jonge dieren (Miceli et al., 2017) niet wordt veroorzaakt door veranderingen in het gebruik van de zintuigen zelf. Deze resultaten geven aan dat postnatale ontwikkeling van een adaptieve motorcontrole een intact serotoninesysteem vereist, en dat zelfs korte veranderingen binnen de serotonine-communicatie tijdens de vroege ontwikkeling al langdurige sensomotorische verstoringen teweeg kunnen brengen in het volwassen dier. Experimenten met het computermodel van het sensomotorische systeem van de snorharen laten zien dat deze observaties kunnen worden verklaard door middel van een holistisch netwerkmodel van de sensomotorische computaties, en laten zien hoe de veranderingen in het netwerk de mechanische kracht bij het snorhaarfollikel beïnvloeden en de resolutie van de tastzin verminderen.

In **Hoofdstuk 5** wordt het onderzoek in dit proefschrift in z'n geheel nabesproken en stel ik dat objectlokalisatie een probleem is dat adaptieve motorcontrole aangaat en

dat verklaard kan worden door middel van Bayesische filtering. Met ondersteuning van de empirische observaties in dit proefschrift stel ik dat het brein dit probleem oplost door middel van een herhalend proces met een dynamische vernieuwing van een intern model van de waargenomen wereld. Verder stel ik dat adaptief gebruik van de snorharen de zekerheid tijdens objectlokalisatie vergroot door de hoeveelheid ruis te verminderen. Bij het uitvoeren van deze computaties zet het brein sensorische informatie eerst om in egocentrische coördinaten en gebruikt vervolgens aangeleerde transferfuncties om sensorische informatie te vertalen naar motorische acties. Het gedrag dat uit deze berekeningen voortkomt is de adaptieve sensomotorische controle voor navigatie.

List of publications

LIST OF PUBLICATIONS

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1) *Reduced inhibition within layer IV of Sert Knockout rat barrel cortex is associated with faster sensory integration.* Miceli S, Nadif Kasri N, Joosten J, Huang C, Kepser L, Proville R, Selten MM, van Eijs F, **Azarfar A,** Homberg JR, Celikel T, Schubert D. Cereb Cortex. 2017 Feb 1;27(2):933-949. doi: 10.1093/cercor/bhx016.
2) *High-precision spatial localization of mouse vocalizations during socialinteraction.* Heckman JJ, Proville R, Heckman GJ, **Azarfar A,** Celikel T, Englitz B. Sci Rep. 2017 Jun 7;7(1):3017. doi: 10.1038/s41598-017-02954-z.
3) *Neural coding: A single neuron's perspective.* **Azarfar A,** Calcini N, Huang C, Zeldenrust F, Celikel T. Neuroscience and Biobehavioral reviews, 2018 Sep 15; 94:238-247. doi: 10.1016/j.neubiorev.2018.09.007
4) *An open-source high-speed infrared videography database to study the principles of active sensing in freely navigating rodents.* **Azarfar A,** Zhang Y, Alishbayli A, Miceli S, Kepser L, Homberg J, Schubert D, Proville R, Celikel T. Gigascience, in press
5) Tracking animal uncertainty for automated robotic *animal training.* Herman, DH **Azarfar A**, Celikel T. Submitted
6) *Development of adaptive motor control for active sensing.* **Azarfar A,** Celikel T. Submitted
7) *Transient perturbation with serotonergic signaling during postnatal development impairs sensorimotor control in adulthood.* **Azarfar A,** Zhang Y, Alishbayli A, Celikel T. Submitted
8) *Simultaneous representation of sensory information and stimulus expectation in the somatosensory cortex.* Zhang, Y. **Azarfar A,** Proville R, Brouns T, Celikel T. In submission
9) *Adaptive motor control as* a filtering process. Azarfar A, Celikel T. In preparation

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Curriculum Vitae

CURRICULUM VITAE

Alireza Azarfar was born in Tehran, Iran. He studied Electronic Engineering at Shahid Beheshti University, Tehran, Iran, during which he worked on audio signal processing. In 2010 he moved to portugal to pursue his master in Integrated Master of Electronic and Telecommunication, where he worked on sound source localization and recognition for humanoid robots using biologically inspired system utilizing spiking neural network. Beginning 2013 he moved to Nijmegen in the Netherlands to pursue the doctoral studies in the Donders Graduate School of the Radboud University where he worked under supervision of prof.dr. Tansu Celikel on adaptive sensorimotor control for navigation. Most of the scientific studies performed during this period are described in the present manuscript.

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Positions outside academia spread among the following sectors:

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- specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy,
- higher education as coordinators or lecturers.

A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

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